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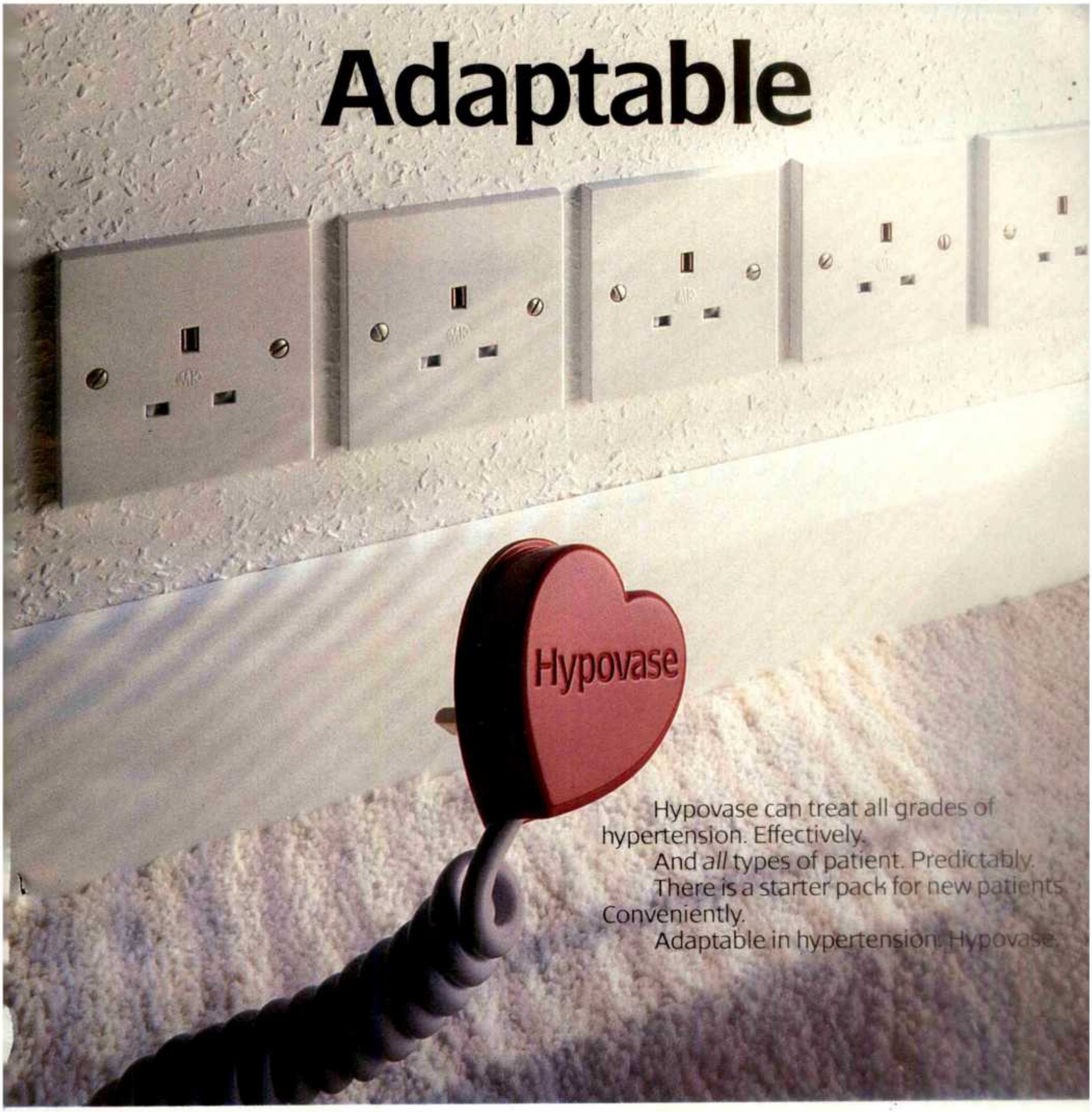

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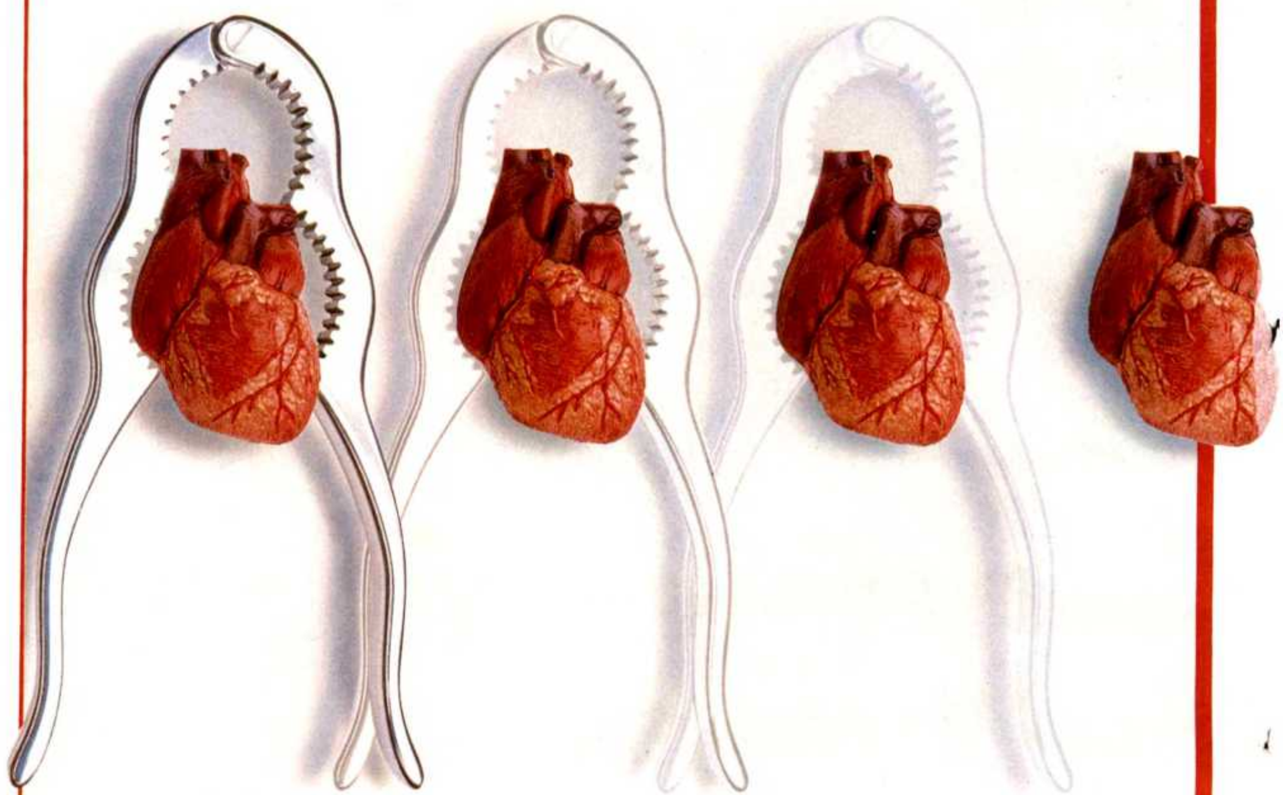

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Jubilee Editorial

Cardiac imaging 50 years on

A L MUIR

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When the Cardiac Club became the British Cardiac Society 50 years ago radiological examination was the only means of imaging the heart; however, the physical basis of many of the newer forms of imaging was already established. Roentgen's exciting discovery of 1895 stimulated Williams to report on *x* ray examination of the heart the following year. He noted that "the pulsations of the heart may be followed with the fluoroscope, not only ventricular, but also auricular contractions and dilatations" and he went on to comment that the first medical case he examined was that of a man with an enlarged heart (seven inches in transverse diameter).[1] That he managed to image the heart, although the man was wearing two shirts and a waistcoat, speaks more for his skill than the sartorial style of his subject. Roentgenology of the skeleton and chest rapidly progressed, although xenophobia during the first world war changed the name of the discipline to radiology. Radiological examination of the heart was slow to spread, however, and as late as 1920 Sir James MacKenzie wrote "Indeed I am doubtful if an *x*-ray examination of the heart has ever thrown the slightest light on any cardiac condition".[2]

But radiology did flourish and by 1933 John Parkinson and Crichton Bramwell, both members of the Cardiac Club, had, with Peter Kerley, written three important consecutive papers on cardiac radiology in the *British Medical Journal*.[3-5] By 1937 the British Association of Radiologists had been formed and in November of that year its first fellowship examinations were held.[6] There may still have been controversy about whether an *x* ray picture was a radiograph or a radiogram[7] but radiology of the heart was well established. In 1937 Roesler published his book *Clinical Roentgenology of the Cardiovascular System*,[8] and in 1939 the first volume of the *British Heart Journal* contained a detailed radiological account of the volumetric reconstruction of the heart in health and disease by Spillane who wrote that "Radiological study of the heart has now become a well recognised and valuable procedure in the investigation of a cardiac patient".[9]

Early imaging techniques

Much of radiological investigation was done by fluoroscopy, and the red goggles used as an aid to dark adaptation became part of the practising cardiologist's uniform. Despite the risk of considerable exposure to radiation the practice of fluoroscopic examination of the heart persisted until the 1960s.[10] The size and shape of the heart were recorded on a chest film by a process sometimes referred to as teleradiography because the patient and film were positioned 300 cm from the tube, a distance much greater than used for fluoroscopy. The motion of the heart in systole and diastole could be illustrated by kymography. *X* rays were passed through the chest to a film which moved at a uniform rate behind a grid of lead strips.

In 1937 angiography was in its infancy. Forssmann had already recognised the potential of his method of catheterisation for demonstrating the anatomy of the heart and great vessels. In 1931 he used contrast material to visualise the heart chambers in a dog.[11] In the same year Moniz, de Carvalho, and Lima of Lisbon injected sodium iodide into the superior vena cava or the right atrium to produce images of the pulmonary circulation in man.[12] Late in 1937 Castellanos, Pereiras, and Garcia, the Cuban pioneers, reported the use of contrast angiocardiography in the diagnosis of congenital heart disease.[13 14] The subsequent rapid progress in cardiac angiography owes much to these and other pio-

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neers but also to developments in fluoroscopy and in contrast agents. Thorotrast (thorium dioxide) was an early popular contrast agent but by 1937 the potential hazards of its radioactivity were recognised[8] and diotrast then became the most widely used agent for angiography. The safety of modern contrast agents of low osmolality was still a long way off.[15]

In 1945 Radner reported on his attempt to visualise the coronary arteries by inserting a 1·5 mm needle through the manubrium sterni into the ascending aorta and injecting contrast material (thorotrast).[16] After this report demonstration of the coronary arteries was attempted by various techniques but it was not until selective catheterisation was developed by Sones *et al*[17] and the modified transfemoral approach was introduced by Judkins with thermoplastic preformed catheters that coronary arteriography became an established technique.[18]

Analysis of images

The nineteenth century mathematician Charles Babbage is often credited with early attempts to devise a computer; none the less digital computers did not become available till the late 1950s. The transistor was introduced to the commercial world in the early 1960s and the resulting progress in digital computing was so rapid that today it is difficult to conceive of imaging without the ubiquitous computer. Subtraction imaging, based on the difference between a mask image and the contrast image, had been used intermittently in radiology but once the image could be digitised subtraction angiography became comparatively easy. Subtraction angiography has been used to detect regional ventricular dysfunction at rest and during exercise.[19] Initially, it was thought that this technique might avoid selective catheterisation; this has been achieved in only a limited number of applications, such as carotid angiography,[20] but subtraction angiography can be used to produce images with high definition, and its full potential in angiography has not yet been realised. Digital radiology may also produce a further revolution in our ability to store and retrieve radiographs so that the "missing *x* ray" may be a thing of the past.

Another outgrowth of digital technology was the development of computed tomography. When Ambrose and Hounsfield first demonstrated the technique[21] it was clear that there was to be a revolution in neuroradiology. The very long scan times meant that their technique could not be readily applied to the heart, and even the newer machines with a scan time of 2–5 seconds limited its use in cardiology. Heat load limitations and the angular momentum of rotating *x* ray tubes made it necessary to adopt an alternative strategy. The *x* ray beam has been replaced with a magnetically reflected electron beam so the ultimate scan speed is limited only by the need to obtain sufficient photons in a short time. Exposure times of 50 ms are now possible and computed tomographic cineangiography has been used in a number of centres to demonstrate detailed cardiac anatomy. Myocardial perfusion can be assessed by examining thin slices of myocardium and noting the changes in density of injected contrast agent. Computed tomographic cineangiography appears to be useful in demonstrating graft patency.[22]

Ultrasonography and Doppler

The rapid developments in electronics and computing stimulated the use of other physical phenomena to image the heart. Jacques and Pierre Curie described the production of very high frequency sound waves from piezoelectric crystals in 1880[23] and by the mid 1930s ultrasound was being applied to detect flaws in metals. The technique of sonar (sound navigation and ranging), conceived after the sinking of the Titanic and originally developed in the first world war, was important in the detection of submarines in the second world war. Ultrasound was first used medically in an attempt to locate brain tumours.[24] In Britain Donald pioneered the use of ultrasound in obstetrics and gynaecology[25] and shortly afterwards the technique began to be used for investigation of heart disease. Early work used ultrasound in the same way as *x* rays, collecting the signal once it had passed through the chest, but this was abandoned in favour of pulsed reflected ultrasound. Edler in Sweden did much to develop the method[26]; he used it to recognise the abnormal motion of the anterior leaflet of the mitral valve in mitral stenosis. By the late 1960s M mode echocardiography was being used to identify valve function,[27] to detect pericardial effusions,[28] and to diagnose hypertrophic obstructive cardiomyopathy[29] and left atrial myxoma.[30] Subsequent developments in real time and Doppler echocardiography have made ultrasound the first diagnostic procedure in the investigation of a wide range of cardiac conditions. Fetal ultrasound investigation can detect congenital heart disease in utero[31]—a long step forward from the pioneering angiograms of Castellanos and coworkers.[13 14]

Radionuclide imaging

In 1937 few clinicians would have contemplated using radionuclides in cardiovascular investigation, but 10 years before Blumgart and Weiss had described the injection of radium C salt into an arm vein; they timed the arrival of the radioactivity in the artery of the opposite arm by the response of a Wilson cloud chamber.[32] Radionuclide imaging of the cardiovascular system had to await the development of improved imaging devices. Rejali and colleagues used a rectilinear scanner to investigate blood pools of the thorax and abdomen.[33] The introduction of the large crystal scintillation camera[34] and technetium-99m labelled tracers made it possible to view the passage of a tracer bolus through the central venous and arterial circulations in a series of camera images.[35] The development of image processing with computers and the concept of cardiac gating led to the development of techniques for estimation of cardiac output and left ventricular ejection fraction. Techniques have been developed to quantify valve regurgitation and estimate left to right or right to left shunting, and further processing of ventricular images has produced a whole series of function images designed to assist in interpretation of regional abnormalities. Kety used radioactive sodium to determine blood flow in the myocardium.[36] Others have injected diffusible tracers such as xenon-133 or krypton-85 into the coronary artery or into the heart muscle itself and have used the disappearance or wash out of radioactivity as an index of tissue blood flow.

Cannon *et al* used a multicrystal scintillation camera to derive myocardial blood flow from regions corresponding to each of the camera crystals.[37] The suitability of a series of intracellular cation analogues of potassium for identifying perfused myocardium was investigated. Potassium-43 had some success but this was replaced by thallium-201, which is now widely used by many groups, particularly to demonstrate areas of transient ischaemia after exercise. There are still limitations to thallium myocardial scintigraphy and newer technetium labelled compounds are being examined and show some promise.[38] The development of positron emission tomography using carbon-11, oxygen-15, nitrogen-13, or fluorine-18 allows imaging of myocardial metabolism, and this technique promises to be useful for the investigation of regional abnormalities in perfusion and metabolism.[39] Positron emission tomography gives a very precise spatial resolution and it has encouraged the development of three dimensional reconstruction techniques for gamma emitting isotopes. This development of single photon emission computed tomography is a cheaper option than positron emission tomography and is more likely to be used in the investigation of cardiovascular disease in the near future.

Magnetic resonance imaging

Founding members of the British Cardiac Society are unlikely to have paid great attention to a paper published in 1936 by Gorter in which he reported his unsuccessful attempts to find resonance of lithium-7 nuclei in crystalline lithium fluoride.[40] And in 1946 members may have missed reports of the successful demonstration of nuclear magnetic resonance in letters to *Physical Review* by Purcell, Torrey, and Pound and by Bloch, Hansen, and Packard,[41 42] but they will have noted the award of the 1952 Nobel prize for Physics to Bloch and Purcell. Nuclear magnetic resonance was used initially in chemistry and soon after it was applied to biochemistry. The metabolism of human muscle can be studied by nuclear magnetic resonance spectroscopy with phosphorus-31 and as the spatial resolution of the technique improves it should lead to an understanding of altered myocardial biochemistry in heart diseases.[43]

In 1973 Lauterbur described the concept of imaging with nuclear magnetic resonance.[44] He recognised that the nuclear magnetic resonance spectrum was a one dimensional projection of nuclear density along the magnetic field gradient. By applying the gradient in a series of directions he was able to obtain two dimensional images using a mathematical back projection method similar to that used for computed tomographic *x* ray imaging. In 1977 Damadian and colleagues provided the first in vivo proton images of the human heart.[45] Like ultrasound, magnetic resonance imaging does not expose the patient to ionising radiation but in contrast with ultrasound the radio waves penetrate all the tissue including air and bone. Images can be made in any plane. Image quality has improved enormously in recent years and it is possible to demonstrate detailed anatomy and function by nuclear magnetic resonance.[46] The same techniques can be used to demonstrate blood flow[47 48] and studies of anatomy and function are becoming a practical proposition. Another attraction of magnetic resonance imaging is its ability to document altered tissue constituents; also myocardial changes after infarction are clearly visible.[49] These changes were thought to be due to changes in tissue water but probably also reflect the process of cellular infiltration and repair.[50]

Modern imaging now provides detailed knowledge of disordered anatomy and physiology in a manner that it was impossible to predict in 1937. Many of the methods are expensive, with some there is still considerable exposure to radiation of the patient and staff, and some are still at a very early stage of development. Today we must learn to use the available imaging techniques wisely. Tomorrow we shall have to assimilate the best of the newer methods and discard the others. It would be foolish to predict the state of imaging in 2037. Which of today's methods will still be in use? Will imaging be based on a physical phenomenon yet to be explored?

References

1 Williams FH. Notes on *x*-rays in medicine. *Trans Assoc Am Physicians* 1896;**xi**:375–82.

2 Mackenzie J. Chronic diseases of the heart. In: Christian HA, Mackenzie J, eds. *The Oxford medicine.* Oxford: Oxford University Press, 1920:387–492.

3 Parkinson J. Radiology of heart disease. *Br Med J* 1933; **ii**:591–4.

4 Kerley P. Radiology in heart disease. *Br Med J* 1933; **ii**:594–7.

5 Bramwell C. Radiology in heart disease. *Br Med J* 1933;**ii**:597–9.

6 Anonymous. Radiology and its relation to medicine. *Br Med J* 1937;**i**:564–5.

7 Boulton Myles R. Radiograph or radiogram [Letter]. *Br Med J* 1937;**i**:530.

8 Roesler H. *Clinical roentgenology of the cardiovascular system.* Springfield, Illinois: Charles C Thomas, 1937.

9 Spillane JD. Volumetric reconstruction of the heart in health and in disease: a radiological study. *Br Heart J* 1939;**1**:333–44.

10 Cooley RN, Schreiber MH. *Radiology of the heart and great vessels.* Baltimore: Williams and Wilkins, 1967.

11 Forssmann W. Ueber Kontrast darstellung der Hohlen des lebenden rechten Herzens und der Lungenschlagader. *Munch med Wschr* 1931;**78**:489–92.

12 Moniz E, de Carvalho L, Lima A. Angiopneumographie. *Presse Med* 1931;**39**:996–9.

13 Castellanos A, Pereiras R, Garcia A. La angiocardiographia radio-opaca. *Archos Soc Estu clin Habana* 1937;**31**:523–96.

14 de Los Reyes RP, Castellanos A, Pereiras R. Angiography and its value. *Am Heart J* 1943;**25**:298–306.

15 Hayward R, Dawson P. Contrast agents in angiocardiography. *Br Heart J* 1984;**52**:361–8.

16 Radner S. Attempt at roentgenologic visualization of the coronary blood vessels in man. *Acta Radiol* 1945;**26**:497–502.

17 Sones FM Jr, Shirley EK, Proudfit WL, Westcott RN. Cine-coronary arteriography. *Circulation* 1959;**20**: 773–4.

18 Judkins MP. Selective coronary angiography. A percutaneous transfemoral technic. *Radiology* 1967; **89**:815–24.

19 Detrano R, Yiannikas J, Simpfendorfer C, Hobbs RE, Salcedo EE. Exercise digital subtraction ventriculography for the detection of ischaemic wall motion abnormalities in patients without myocardial infarction. *Br Heart J* 1986;**56**:131–7.

20 Seeger JF, Carmody RF. Digital subtraction angiography of the arteries of the head and neck. *Radiol Clin North Am* 1985;**23**:193–210.

21 Ambrose J, Hounsfield G. Computerised transverse axial tomography. *Br J Radiol* 1973;**46**:148–9.

22 Lipton MJ. Quantitation of cardiac function by cine-CT. *Radiol Clin North Am.* 1985;**23**:613–26.

23 Curie J, Curie P. Sur l'électricité polaire dans les cristaux hémiédres à face inclinées. *CR Seances Acad Sci* 1880;**91**:383–9.

24 Dussik KT. Uber die Moglichkeit hochfrequente mechanische Schwingungen als diagnostisches Hilfsmittel zu verwerten. *Z ges Neurol Psychiat* 1952;**174**:153–68.

25 Donald I, MacVicar J, Brown TG. Investigation of abdominal masses by pulsed ultrasound. *Lancet* 1958;**i**:1188–94.

26 Edler I. Diagnostic use of ultrasound. *Acta Med Scand [Suppl]* 1955;**32**:306–8.

27 Edler I, Gustofson A. Ultrasonic cardiogram in mitral stenosis. *Acta Med Scand* 1957;**159**:85–90.

28 Moss AJ, Bruhn F. The echocardiogram: an ultrasound technic for the detection of pericardial effusion. *N Engl J Med* 1966;**274**:380–4.

29 Popp RL, Harrison DC. Ultrasound in the diagnosis of and evaluation of therapy of idiopathic hypertrophic subaortic stenosis. *Circulation* 1969;**40**:905–14.

30 Wolfe SB, Popp RL, Feigenbaum H. Diagnosis of atrial tumours by ultrasound. *Circulation* 1969;**39**:615–22.

31 Allan LD, Tynan MJ, Campbell S, Wilkinson JL, Anderson RH. Echocardiographic and anatomical correlates in the fetus. *Br Heart J* 1980;**44**:444–51.

32 Blumgart HL, Weiss S. Studies on the velocity of blood flow. *J Clin Invest* 1927;**4**:15–31.

33 Rejali AM, MacIntyre WJ, Friedell HL. Radioisotope method of visualisation of blood pool. *Am J Roentgenol* 1958;**79**:129–37.

34 Anger HO. Gamma ray and positron scintillation camera. *Nucleonics* 1963;**21**:56–7.

35 Bonte FJ, Christensen EE, Curry TS. Technetium-99 pertechnetate angiocardiography in the diagnosis of superior mediastinal masses and pericardial effusions. *Am J Roentgenol* 1969;**107**:404–12.

36 Kety SS. Measurement of regional circulation by the local clearance of radioactive sodium. *Am Heart J* 1949;**38**:321–8

37 Cannon EJ, Dell RB, Dwyer EM. Measurement of regional myocardial perfusion in man with 133 Xenon and a scintillation camera. *J Clin Invest* 1972;**51**:964–77.

38 Holman BL, Sporn V, Jones AG, *et al.* Myocardial imaging with technetium-99m CPI: initial experience in the human. *J Nucl Med* 1987;**28**:13–8.

39 Jones T. Positron emission tomography. *Br Med Bull* 1980;**36**:231–6.

40 Gorter CJ. Negative results of an attempt to detect nuclear magnetic spins. *Physica* 1936;**3**:995–8.

41 Purcell EM, Torrey HC, Pound RV. Resonance absorption by nuclear magnetic moments in a solid. *Phys Rev* 1946;**69**:37–8

42 Bloch F, Hansen WW, Packard M. Nuclear induction. *Phys Rev* 1946;**69**:127.

43 Radda GK. Potential and limitations of nuclear magnetic resonance for the cardiologist. *Br Heart J* 1983;**50**:197–201.

44 Lauterbur PC. Image formation by induced local interactions: examples employing nuclear magnetic reso-

nance. *Nature* 1973;**242**:190–1.

45 Damadian R, Goldsmith M, Minkoff L. NMR in cancer: fonar image of the live human body. *Physiol Chem Phys* 1977;**9**:97–108.

46 Underwood SR, Rees RSO, Savage PE, *et al.* Assessment of regional left ventricular function by magnetic resonance. *Br Heart J* 1986;**56**:334–40.

47 Ridgway JP, Smith MA. A technique for velocity imaging using magnetic resonance imaging. *Br J Radiol* 1986,**59**·603–7.

48 Klipstein RH, Firmin DN, Underwood SR, Nayler GL, Rees RSO, Longmore DB Colour display of quantitative blood flow and cardiac anatomy in a single magnetic resonance cine loop. *Br J Radiol* 1987;**60**:105–11.

49 Been M, Ridgeway JP, Douglas RHB, *et al.* Characterisation of acute myocardial infarction by gated magnetic resonance imaging. *Lancet* 1985;**ii**:348–50.

50 Muir AL, Smith MA, Been M, *et al* Sequential changes in T_1 in man following acute myocardial infarction. Book of Abstracts Fifth Annual Meeting Society of Magnetic Resonance in Medicine 1986;1:237–8 Berkeley, California: Society of Magnetic Resonance in Medicine.

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Editorial

Acute myocarditis: a diagnostic dilemma

MARGARET BILLINGHAM

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Myocarditis, an inflammatory process affecting the myocardium, may be caused by any bacterial, viral, rickettsial, mycotic, or parasitic organism. In Europe and in the United States, however, most cases of acute myocarditis seem to be caused by viruses. It is often difficult to prove the viral aetiology in cases of myocarditis and such cases are often referred to as idiopathic myocarditis. The Coxsackie B enterovirus is especially cardiotropic in man, although Coxsackie pericarditis is thought to be more common than Coxsackie myocarditis. Coxsackie virus infections commonly appear as epidemics, particularly in the summer and autumn. Coxsackie virus types B1 to 5 and A4 and 16 are the strains most commonly implicated. The echovirus group of enteroviruses, especially types 9, 11, and 22, can also cause acute myopericarditis. Even when a causative organism is isolated it is often not known whether direct invasion and tissue damage by the infectious agent or a toxic, allergic, or hypersensitivity response to this agent is responsible for the clinical, electrophysiological, haemodynamic, and morphological manifestations of myocarditis.[1] Although raised titres of neutralising antibody in the serum may suggest viral myocarditis they are not necessarily diagnostic. Also viral particles have never been seen unequivocally in the myocardium except cytomegalovirus in immunocompromised hosts. The clinical diagnosis of myocarditis is difficult, if not impossible. For this reason, the incidence and course of the disease have not been established. Some published reports suggest that myocarditis improves when immunosuppressive agents are given; however, others suggest that steroid treatment may increase the adverse effects of myocarditis or even accelerate its course.

If treatment is to be attempted accurate diagnosis of myocarditis becomes even more important. The widespread use of multiple endomyocardial biopsies raised hopes that it would be possible to diagnose myocarditis more accurately if a histopathological examination showed a definite inflammatory infiltration of the myocardium. Unfortunately, it now appears that the use of the endomyocardial biopsy in the diagnosis of acute myocarditis may have raised more problems than it has solved.

The role of the endomyocardial biopsy in viral myocarditis

Endomyocardial biopsy is now an established and safe procedure in experienced hands[2 3] and should be well suited to the definitive morphological diagnosis of myocarditis. The role of the biopsy, which seemed obvious and exciting, may be summarised as: (*a*) to identify the inflammatory infiltrate within the myocardium; (*b*) to rule out any other causes of myocardial disease which might clinically mimic viral myocarditis, such as sarcoidosis, hypersensitivity reaction (eosinophilic myocarditis), or idiopathic dilated cardiomyopathy; (*c*) to follow the development of a dilated cardiomyopathy in cases of confirmed viral myocarditis (a sequence of events long suspected, but apart from anecdotes, never satisfactorily proved); and (*d*) to investigate the effect of treatment, particularly the controversial one of immunosuppression.

Pitfalls of endomyocardial biopsy in acute myocarditis

There are many reasons why interpretation of myocarditis by endomyocardial biopsy is difficult. Some, such as variation in sample size owing to the use of different bioptomes, obvious sampling error, and the failure to take into account other causes of lymphocytic infiltrates in the myocardium have already been noted.[4] Patients dying of myocarditis were

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known to have a fulminant interstitial infiltrate of inflammatory cells, usually a mixed cell infiltrate together with necrosis of the myocardium, but the early morphological stages of this disease were unclear. The question of whether focal clusters of inflammatory cells represented "early" myocarditis became an issue. This question was partially resolved when several large necropsy series on young accident victims (presumed to be healthy) revealed lymphocytic infiltrations in 4–10% of cases.[5-7]

As well as the normal occurrence of lymphocytes in the heart, small collections of inflammatory cells with focal myocyte necrosis are known to be a result of the "catecholamine" effect of stress or vasopressor agents. Some pathologists felt that in the setting of "clinical" myocarditis these focal collections of inflammatory cells were important and myocarditis was diagnosed even though it is known that a classical history and symptoms of myocarditis are frequently spurious. More important, however, was the fact that most endomyocardial biopsies were performed on patients who presented in left heart failure, which is unlikely to be caused by focal aggregates of inflammatory cells even if focal myocyte damage is present. There is now a vast experience (over 10 000 endomyocardial biopsy specimens in our own centre alone) with biopsy specimens from cardiac allograft recipients with acute rejection, which is morphologically indistinguishable from viral myocarditis and which is therefore a good model of viral myocarditis. From this experience we have learned that focal myocyte necrosis and inflammatory infiltrates do not result in heart failure. In fact, it is clear that only fulminant, diffuse infiltrates that are present in every biopsy fragment lead to heart failure. This experience makes a strong case against labelling focal infiltrates as myocarditis; if the patient is already in heart failure another cause should be looked for. Small focal collections of acute or chronic inflammatory cells in isolated microscopic fields must not be over emphasised if clinical credibility is to be retained.[8]

Dilated congestive cardiomyopathy may present suddenly in young athletic patients without previous symptoms but with a history of "flu" symptoms resembling acute myocarditis. Cardiac biopsy specimens from these patients also may show a considerable number of lymphocytes in the myocardium. In one study 25% of biopsy specimens from patients with dilated congestive cardiomyopathy contained considerable numbers of lymphocytes,[9] and 87% of 108 hearts from patients with end stage cardiomyopathies who were undergoing transplantation showed foci of mononuclear cells.[10] Biopsy specimens from patients with dilated congestive cardiomyopathy have been mistakenly diagnosed as myocarditis because pathologists have failed to recognise the "background" of the pronounced hypertrophy with large bizarre shaped nuclei and fibrosis that distinguishes biopsy specimens from patients without coronary disease who have dilated congestive cardiomyopathy.

The last two paragraphs summarise some of the more important reasons why there is overdiagnosis of acute viral myocarditis in many endomyocardial biopsy specimens. The reported frequency of "biopsy proven" myocarditis from various centres ranges from 3% to 41% and 63%[11 12] or even higher. This causes difficulties not only for clinicians treating these patients but also because the results of studies undertaken on patients supposed to have "biopsy proven" myocarditis may be misinterpreted. Concern about such misinformation, together with the need to do a good randomised multicentre study on the possible beneficial effect of immunosuppression on myocarditis, led to a meeting in Dallas, Texas, in March 1984 of eight cardiac pathologists with experience and interest in the interpretation of endomyocardial biopsy specimens. The Dallas criteria for a histopathological definition and classification of myocarditis were formulated at this meeting.

The Dallas classification

Because the clinical symptoms of acute myocarditis can be mimicked by other cardiac diseases entry into any trial of immunosuppressive treatment for acute myocarditis must depend on an endomyocardial biopsy specimen that shows acute myocarditis. Because there were no uniform diagnostic criteria for acute myocarditis it was necessary, for the purposes of the trial, to attempt a classification that any pathologist could follow. In brief, the goals of the group were (*a*) to produce a morphological definition of myocarditis, (*b*) to develop histopathological criteria for the diagnosis of myocarditis, (*c*) to establish a simple reproducible working classification, (*d*) to outline the problems and pitfalls of establishing the diagnosis of myocarditis, (*e*) to assess the applicability and reproducibility of the classification system itself, and (*f*) to make this information available to other pathologists and clinicians. This goal was attained and a working classification and definition was published.[4]

There are three diagnostic categories of myocarditis at initial biopsy:

(a) Active myocarditis (with or without fibrosis).—Both an inflammatory infiltrate and damage of the adjacent myocytes are required for this diagnosis. The damage may be frank necrosis but

but may consist of vacuolisation, irregular cellular outlines, and cellular disruption with lymphocytes closely applied to the cell surface. The uninvolved myocardium often appears normal.

(b) Borderline myocarditis (not diagnostic, requires repeat biopsy).—This term implies that the inflammatory infiltrate is too sparse or that myocyte damage is not seen on light microscopy. Additional cuts of the original biopsy specimens may demonstrate diagnostic changes, in which active myocarditis can be diagnosed without a repeat biopsy.

(c) No evidence of myocarditis.

Three categories will be used to classify the results of subsequent biopsies:

(a) Ongoing (persistent) myocarditis.—This diagnosis is made when the degree of abnormality is the same or worse than that of the original biopsy specimen.

(b) Resolving myocarditis.—This diagnosis is made when the inflammatory infiltrate is less than in (*a*) and reparative changes are evident.

(c) Resolved myocarditis.—No inflammatory infiltrate remains and there is no evidence of ongoing cellular necrosis.

It must be emphasised that this exercise was prompted, convened, and executed by pathologists in the multicentre trial. It was not meant to establish a definite classification of acute myocarditis; rather the purpose was to test some of the problems of diagnosis—for example are small foci of inflammatory cells in the heart a manifestation of myocarditis?

The Dallas criteria, however, have been misunderstood and misrepresented as a classification that sometimes is used as a *sine qua non* of the histological diagnosis of myocarditis. But, as clearly stated in the report, our goal was to "establish a simple reproducible working classification" in order to "assess the applicability and reproducibility of the classification system." Further it was stated that the purpose of the report was to present a purely morphological classification and definition of myocarditis that would be workable and simple for those participating in the multicentre trial. We also stated that "histology itself may prove not to be the 'gold standard' for the diagnosis of myocarditis and that other features such as physiologic, biologic, biochemical, or immunologic parameters in the future may be shown to be more accurate in assessing the presence, prognosis, and treatment of the disease."

Pathologists using the Dallas classification should be aware that it was devised to achieve more uniform diagnosis and that the classification itself has yet to be tested. Until the Multi-Centre Myocarditis Trial is finished, assuming that sufficient myocarditis positive specimens are collected, we will not know whether the small focal myocardial lesions are indeed harbingers of myocarditis or whether they resolve spontaneously without sequelae. Only then can we assess the value of the Dallas classification.

Endomyocardial biopsy, carefully performed and intelligently examined, is a useful diagnostic tool for the study and management of many cardiac disease states. Many new and useful facts have emerged from the use of the biopsy and there is still much more to be learned from it. We must take care not to jeopardise the credibility of cardiac biopsy by trying to use it inappropriately and by not being mindful of its limitations.

References

1 Wenger NK, Abelmann WH, Roberts WC. Myocardial disease. In: Hurst VW, ed. *Myocarditis in the heart.* New York: McGraw-Hill, 1982:1278.

2 Ursell PC, Fenoglio JJ Jr. Endomyocardial biopsy: established diagnostic procedure. *Chest* 1983;**84**:122–3.

3 Mason JW. Endomyocardial biopsy: the balance of success and failure (perspective). *Circulation* 1985; 71:185–8.

4 Aretz HT, Billingham ME, Edwards WD, *et al.* Myocarditis, a histopathologic definition and classification. *Am J Cardiovasc Pathol* 1987;1:3–14.

5 Linder J, Cassling RS, Rogler WC, *et al.* Immunohistochemical characterization of lymphocytes in uninflamed ventricular myocardium: implications for myocarditis. *Arch Pathol Lab Med* 1985;**109**:917–20.

6 Stevens PJ, Ground KEU. Occurrence and significance of myocarditis in trauma. *Aerospace Med* 1970; 41:776–80.

7 Tazelaar HD, Billingham ME. Myocardial lymphocytes; fact, fancy or myocarditis? *Am J Cardiovasc Pathol* 1987;1:47–50.

8 Davies MJ. Myocarditis. In: Pomerance A, Davies MJ, eds. *The pathology of the heart.* Oxford. Blackwell Scientific Publications, 1975:193–210.

9 Baandrup U, Olsen EGJ. Critical analysis of endomyocardial biopsies from patients suspected of having cardiomyopathy. I. Morphological and morphometric aspects. *Br Heart J* 1981;**45**:475–86.

10 Tazelaar H, Billingham M. Leukocytic infiltrates in idiopathic dilated cardiomyopathy. A source of confusion with active myocarditis. *Am J Surg Pathol* 1986;**10**:405–12.

11 Fenoglio JJ Jr, Ursell PC, Kellog CF, Drusin RE, Weiss MG. Diagnosis and classification of myocarditis by endomyocardial biopsy. *N Engl J Med* 1983;**308**.12–8.

12 Zee-Cheng C-S, Tsai CC, Palmer DC, Codd JE, Pennington DG, Williams CA. High incidence of myocarditis by endomyocardial biopsy in patients with idiopathic congestive cardiomyopathy. *J Am Coll Cardiol* 1984;3:63–70.

Br Heart J 1987;58:9–14

Preoperative myocardial ischaemia: its relation to perioperative infarction

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SUMMARY One hundred consecutive patients undergoing coronary artery bypass surgery were randomly allocated to a preoperative (24 h) intravenous infusion of isosorbide dinitrate (1·5–15 mg/hr) (50 patients) or to placebo (50 patients). The characteristics of the two groups were similar. Evidence of acute myocardial ischaemia was sought by continuous electrocardiographic Holter recordings and acute myocardial infarction by the appearance of new Q waves and increased activity of the creatine kinase MB isoenzyme. Episodes of acute myocardial ischaemia were found in 18% of patients in the control group and in none of those who received isosorbide dinitrate. None the less, the frequency of perioperative myocardial infarction was similar (22% and 18% respectively) in the two groups. Perioperative infarction was significantly more common in women, in patients with unstable angina or poor left ventricular function, in those who had coronary endarterectomy, and in those in whom the aortic clamping time was greater than 50 minutes. These factors may have obscured any effect that prevention of preoperative ischaemia had on perioperative infarction.

Preoperative infusion of isosorbide dinitrate eliminated preoperative ischaemia but did not influence the occurrence of perioperative infarction. The probable benefits of prevention of preoperative ischaemia on postoperative left ventricular function, which is a determinant of long term survival, remain to be established.

Myocardial infarction is a frequent complication of aortocoronary saphenous vein grafting and an important cause of perioperative death and long term morbidity.[1-9] The frequency of infarction has been variously reported to be between 4% and 40%, depending to a certain extent on its definition.[3 4 10 11] The established causes are inadequate myocardial protection,[12 13] reperfusion injury,[14] thrombosis of a native coronary artery, and early graft occlusion. Although most infarcts occur during and soon after surgery, others may develop before the operation begins. Prolonged preoperative myocardial ischaemia may be a contributory factor in such patients.

This study was designed to investigate the frequency of preoperative ischaemia, its relation to perioperative infarction, and the effectiveness of isosorbide dinitrate infusion in its control.

Patients and methods

One hundred patients undergoing coronary artery bypass grafting were studied between 1 October 1983 and 30 September 1984. They were randomly allocated to either the control (50 patients) or the infusion (50 patients) groups. The two groups were found to be comparable in terms of age, sex, clinical presentation, risk factors, previous myocardial infarction, left ventricular function, the number of diseased coronary vessels, medical treatment, the number of grafts, and the surgical procedure (table 1). Ninety two per cent of the patients had chronic stable angina that was poorly controlled by medical treatment. Only 8% had unstable angina.

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Table 1 *Patient characteristics*

	Control group	*Infusion group*
Number of patients	50	49
Age range	34–74	39–74
Mean (SD) age	56·0 (9·4)	56·5 (7·9)
Male	38	41
Female	12	8
Total risk factors	63	67
Mean (SD) risk factors	1·5 (1·1)	1·5 (0·8)
Old myocardial infarction	34	33
Unstable angina	3	5
Medical treatment		
β blocker	41	43
Nitrates	46	43
Calcium antagonist	37	38
Disease extent		
Left main stem	2	6
3 vessel disease	29	28
2 vessel disease	15	17
Single vessel disease	6	4
Left ventricular ejection fraction:		
>55%	16	14
Impaired 30–54%	28	28
Poor <30%	6	7
Endarterectomy	10	10
Graft		
Total number	151	159
Mean (SD)	3·0 (1·0)	3·3 (0·8)
1	3	1
2	12	8
3	20	20
4	11	18
5	4	2

PROTOCOL

In all patients a standard preoperative routine was followed. This included a 12 hour preoperative fast, except for the continued administration of antianginal and other necessary drugs. Fifty patients were given an intravenous infusion of isosorbide dinitrate (Cedocard, Tillotts) through a battery powered portable syringe pump for 24 hours before operation. The dose was adjusted to a maximum of 15 mg/hour to maintain a systolic blood pressure of at least 90 mm Hg. There were no untoward side effects but in three patients on a small dose of isosorbide dinitrate the blood pressure dropped during sleep. In these patients the infusion was interrupted at night and resumed in the morning.

The standard cardiopulmonary bypass procedure was used with a flow rate of 2·4 l/min, systemic hypothermia to 27°C, and cold potassium cardioplegia. A small number of patients required additional topical cardiac cooling. The aortic cross clamping time averaged 20 minutes with an additional 10 minutes for each graft and each endarterectomy procedure. On average the perfusion time was 15 minutes longer than the clamping time. An average of 3·2 grafts was placed per patient and 80% of the patients in each group were operated on by the same surgeon.

DETECTION OF ACUTE MYOCARDIAL ISCHAEMIA

In 33 control patients and 34 infusion patients two channel continuous Holter electrocardiographic monitoring with a frequency modulated (Medilog 2, Oxford Instruments) recorder was started 24 hours before surgery and continued until the last possible moment before surgery, including the period of anaesthetic induction. (These two subgroups were also closely comparable in relation to those variables examined in the control and infusion groups.) The recordings were initially examined by visual inspection to detect the presence of transient reversible ST shifts (>0·1 mV horizontal or downsloping ST segment depression, indicating acute myocardial ischaemia). Automatic computer analysis was performed on the positive tapes to give a continuous plot of heart rate, ST segment negative area, and level of the ST segment 80 ms after the J point. In addition, the duration of each ischaemic episode, the total number of episodes, and the total duration of ischaemia were also calculated. The 24 hour distribution of ischaemic attacks and their relation to the time of operation were noted.

DETECTION OF ACUTE MYOCARDIAL INFARCTION

Electrocardiogram

Twelve lead electrocardiograms were recorded before operation, immediately after operation, and again on the first, third, fifth, and tenth days after operation. The development of new abnormal Q waves in at least two leads was regarded as diagnostic of acute myocardial infarction.

Creatine kinase

Venous blood (10 ml) was taken 24 hours before operation, immediately after operation, and one hour and 21 hours after operation for estimation of total creatine kinase and creatine kinase MB. Total creatine kinase activity in serum was measured at 37°C in the presence of N-acetyl cysteine by means of kits (Smith Kline Instruments Co) and a Clinicon Corona Analyser. The reagents conform to the Scandinavian recommended method for the estimation of creatine kinase.

Creatine kinase MB was measured by a N-acetyl cysteine-activated ultraviolet system kit (Boehringer Mannheim). The method is based on the immunoinhibition of creatine kinase M subunit activity followed by estimation of the remaining creatine kinase activity. We confirmed that residual activity was due to creatine kinase MB, and not to the BB isoenzyme by cellulose acetate electrophoresis. A creatine kinase MB activity of 750 IU/l was considered to be diagnostic of myocardial infarction in

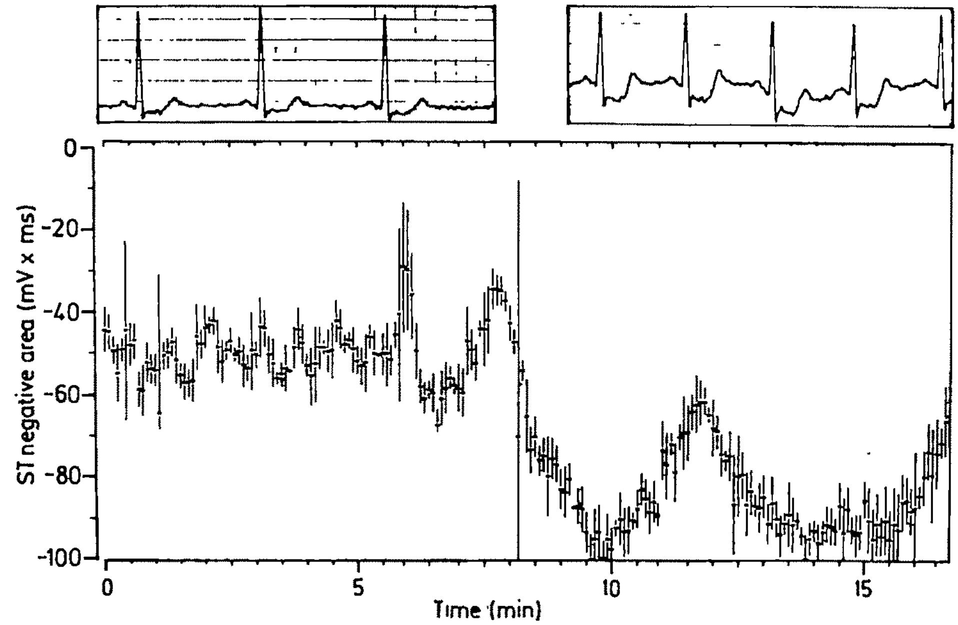

Fig 1 *Part of the original ST segment plot (ST negative area) of the patient with severe preoperative myocardial ischaemia who sustained a perioperative infarction.*

cases with equivocal electrocardiographic changes and in those (two patients) with left bundle branch block.

Results

ACUTE MYOCARDIAL ISCHAEMIA

There were episodes of transient ST segment depression diagnostic of myocardial ischaemia in six (18%) of the 33 patients in the control group and in none of the 34 infusion patients. There was a total of 24 transient ischaemic episodes, varying from five to 27 minutes in duration. The total duration of ischaemia was 329 minutes, varying between five and 110 minutes per patient. A patient who had 110 minutes of preoperative ischaemia (fig 1) died immediately after operation. The creatine kinase MB activity of that patient one hour before operation was normal; however, acute infarction was found at necropsy.

The myocardial ischaemic attacks were distributed throughout the 24 hour period, but they tended to cluster between the hours of five and nine in the morning (fig 2) and to increase in the few hours

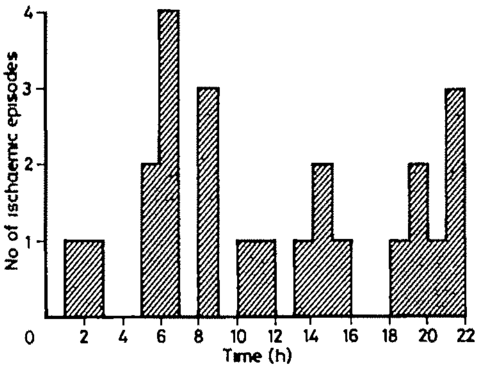

Fig 2 *Diurnal distribution of the total number of attacks of acute myocardial ischaemia in six control patients.*

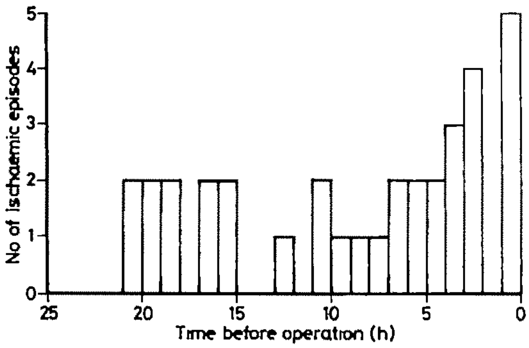

Fig 3 *Distribution of the total number of attacks of acute myocardial ischaemia in six control patients during the 24 hour period preceding operation.*

immediately preceding surgery, including the induction of anaesthesia (fig 3). The total duration of myocardial ischaemia during the first 21 hours was 192 minutes, rising to 137 minutes during the last three hours preceding surgery.

PERIOPERATIVE ACUTE MYOCARDIAL INFARCTION

Twenty patients (20%) sustained a perioperative myocardial infarction, and the electrocardiograms showed that there were two distinct electrocardiographic patterns of myocardial infarction: (*a*) the typical pattern where the appearance of convex ST segment elevation was usually followed (> 12·0 h) later by new Q waves; (*b*) the atypical pattern, where Q waves appeared much earlier (< 6 h) and without preceding ST segment elevation.

Symes *et al* showed that pattern (*a*) is caused by native coronary artery or graft occlusion (occlusive infarction), whereas pattern (*b*) occurs in the absence of vascular occlusion and may be caused by reperfusion injury (reperfusion infarction).[14] Fourteen infarcts occurred within six hours of operation and can be considered as intraoperative events; half of these were typical (occlusion) and half were atypical (reperfusion). Six patients with reperfusion infarction had suffered previous myocardial infarction in the same vascular territory, compared with two who had occlusive infarcts. Table 2 lists the preoperative and operative factors and their relation to infarction.

Table 2 *Relation of perioperative acute myocardial infarction to preoperative and operative factors*

Factor	*No of patients*	*No of infarcts*	%	*p*
Sex:				
Female	20	8	40	
Male	79	11	14	<0·05
Blood pressure:				
Hypertension	33	9	28	
No hypertension	66	11	17	
Hypertension/males	24	4	17	
Hypertension/females	9	5	55	<0·05
Ischaemia				
Preoperative ischaemia	6	2	33	
No preoperative ischaemia	61	10	16	NS
Angina:				
Unstable angina	8	5	62·5	
Stable angina	91	15	16	<0·01
Number of vessels diseased.				
Single	10	1	10	
Double	32	7	22	NS
Triple	57	12	21	
Left main stem stenosis:				
Present	8	3	38	
Absent	91	17	19	NS
Left ventricular function				
Normal (EF ≥ 55%)	25	2	8	
Impaired (EF 30–54%)	61	14	23	<0·05
Poor (EF < 30%)	13	5	39	
Aortic clamping time:				
≥ 50 min	27	10	37	
< 50 min	72	10	13	<0·05
Number of grafts:				
One or two	24	4	17	
Three	40	8	20	NS
Four or five	35	9	23	
Conjunctive endarterectomy				
Present	20	8	40	
Absent	79	12	15	<0·05

EF, ejection fraction.

Three patients (3%) died, all of acute perioperative infarction of the typical (occlusive) type. Two were in the control group; one of these had suffered prolonged preoperative ischaemia (fig 1). The patient in the infusion group developed acute myocardial infarction during the second postoperative day, 36 hours after the end of isosorbide dinitrate infusion, and died.

Discussion

Perioperative acute myocardial infarction is an important factor determining the morbidity and mortality of coronary artery bypass surgery. Recognition and modification of the factors contributing to perioperative infarction may reduce its occurrence.

ACUTE MYOCARDIAL ISCHAEMIA

Almost one fifth (18%) of patients with predominantly stable angina developed appreciable myocardial ischaemia in the hours immediately before operation. Most ischaemic episodes were painless. They increased in frequency and duration as the operation drew near, sometimes appearing for the first time after premedication or during induction of anaesthesia. This increasing tendency for ischaemia to develop might have been related to mounting anxiety in anticipation of surgery or to the haemodynamic changes that accompany induction of anaesthesia. Both factors have been reported to induce myocardial ischaemia.[15] Declining concentrations of antianginal drugs may have been a contributing factor, although in most of our patients drug treatment was continued up to the time of operation. Irrespective of the mechanism of ischaemia, infusion of isosorbide dinitrate completely prevented the occurrence of acute myocardial ischaemia. Despite the prevention of acute myocardial ischaemia infusion of isosorbide dinitrate had no significant effect on the frequency of perioperative infarction. This finding may be the result of the low frequency of preoperative myocardial ischaemia, which occurred in only six patients in this study of patients with predominantly stable angina. Larger numbers of patients or a higher frequency of preoperative myocardial ischaemia, as might be expected in unstable angina, would be required to demonstrate any significant effect. The multiplicity of mechanisms causing perioperative infarction would also tend to obscure any reduction in the frequency of perioperative infarction related to the prevention of preoperative myocardial ischaemia.

PATHOGENESIS OF PERIOPERATIVE INFARCTION

Two distinct patterns of evolution of perioperative infarction were observed electrocardiographically. Similar findings have been reported before.[14] The development of classic ST segment changes evolving into Q wave formation is suggestive of the coagulation necrosis that has been found in association with occluded grafts. The early development of Q waves without previous evolutionary ST changes is compatible with the contraction band necrosis which has been found in association with patent grafts and non-grafted vessels and has been thought to be due to reperfusion injury. Whereas the sudden flux of calcium into cells leads to rapid cellular necrosis in reperfusion injury, the protein denaturation by acidosis and cellular injury by lysosomal enzymes found in coagulation necrosis causes gradual cell death and results in the classic evolutionary changes in the electrocardiogram. Symes *et al* attributed the majority of intraoperative infarcts to reperfusion injury[14] but the electrocardiographic pattern in our patients suggests a frequency of approximately 50%. Intraoperative infarcts often occur as an extension of a previously infarcted territory.

Other factors were clearly associated with perioperative infarction in this study. The high frequency in women may be related to the smaller size of their coronary arteries and saphenous veins. The high frequency associated with endarterectomy has been reported by other workers as has the increased frequency in those with unstable angina and poor left ventricular function.[16-18]

Finally, though the incidence of perioperative infarction does not significantly increase with the number of grafts performed, the speed of operation is important. Those patients with technically difficult operations needed prolonged aortic clamping and they had significantly higher infarction rates (table 2).

Conclusion

A small proportion of patients with predominantly stable angina developed episodes of acute myocardial ischaemia of increasing frequency and duration in the 24 hour period leading up to coronary artery bypass surgery. Although these episodes were abolished by intravenous infusion of isosorbide dinitrate, there was no significant impact on the frequency of perioperative myocardial infarction. This reflects the multifactorial nature of the mechanism of myocardial infarction.

Further study is required to investigate the effect of preoperative ischaemia on perioperative infarction in patients with unstable angina and on postoperative left ventricular function, a determinant of long term prognosis. A further study is in progress in which patient factors, such as endarterectomy, that might obscure the effect of isosorbide dinitrate have been excluded.

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References

1 Rose MR, Glassman E, Isom OW, Spencer FC. Electrocardiographic and serum enzyme changes of myocardial infarction after coronary artery bypass surgery. *Am J Cardiol* 1974;33:215–9.
2 Sternberg L, Wisneski JA, Ullyot DJ, Gertz EW. Significance of new Q waves after aortocoronary bypass surgery. *Circulation* 1975;52:1037–44.
3 Brewer DL, Bilbro RH, Bartel AG. Myocardial infarction as a complication of coronary bypass surgery. *Circulation* 1973;47·58–64.
4 Gray R, Ganz W, Charuzi Y, *et al.* Morbidity and mortality of perioperative myocardial infarction in coronary bypass surgery: a two year follow-up. *Circulation* 1978;58(suppl II):11–8.
5 Conley M, McNeer JF, Wagner G, Ross-Duggan J, Harris P, Rosati R. Prognostic significance of myocardial infarction complicating aortocoronary bypass [Abstract]. *Circulation* 1978;58(suppl II):11–6.
6 Chaitman BR, Alderman EL, Sheffield LT, *et al.* Use of survival analysis to determine the clinical significance of new Q waves after coronary bypass surgery. *Circulation* 1983;67:302–9.
7 Assad-Morell JL, Frye RL, Connolly DC, *et al.* Relation of intraoperative or early postoperative transmural myocardial infarction to patency of aortocoronary bypass grafts and to diseased ungrafted coronary arteries. *Am J Cardiol* 1975;35:767–73.
8 Fennell WH, Chua KG, Cohen L, *et al.* Detection, prediction and significance of perioperative myocardial infarction following aorto-coronary bypass. *J Thorac Cardiovasc Surg* 1979;78:244–53.
9 Oberman A, Cutter G, Kouchoukos N, Allen R, Kitts J, Sheffield T. Survival following perioperative myocardial infarction [Abstract]. *Circulation* 1980;62 (suppl III):94.
10 McIntosh HD, Garcia JA. The first decade of aortocoronary bypass grafting. 1967–1977. *Circulation* 1978;57:405–8.
11 Bassan MM, Oatfield R, Hoffman I, Matloff J, Swan HJC. New Q waves after aortocoronary bypass surgery. Unmasking of an old infarction. *N Engl J Med* 1974;290:349–53.
12 Roe C, Wagner G, Young W, *et al.* Correlation of creatinine kinase isoenzyme MB to postoperative

electrocardiographic diagnosis in patients undergoing coronary artery bypass surgery. *Clin Chem* 1979;25:93–8.

13 Righetti A, Crawford M, O'Rourke R, *et al.* Detection of perioperative myocardial damage after coronary artery bypass graft surgery. *Circulation* 1977;55:173–8.

14 Symes J, Allard J, Huttner I, *et al.* Causes of perioperative myocardial infarction: their identification and prevention. *Can J Surg* 1980;23:438–41.

15 Levinsky L, Lajos TZ, Lee AB, Srinivasan V, Schimert G. Refinements in coronary artery surgery contributing to improved survival. *Thorac Cardiovasc Surg* 1980;28:102–8.

16 Miller CD, Stinson EB, Oyer PE, *et al.* Long-term clinical assessment of the efficacy of adjunctive coronary endarterectomy. *J Thorac Cardiovasc Surg* 1981;81:21–9.

17 Hultgren HN, Pfeifer JF, Angell WW, Lipton MJ, Bilisoly J. Unstable angina: comparison of medical and surgical management. *Am J Cardiol* 1977;39:734–74.

18 Baur HR, Peterson TA, Arnar O, Gannon PG, Gobel FL. Predictors of perioperative myocardial infarction in coronary artery operation. *Ann Thorac Surg* 1981;31:36–44.

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Acceleration time in the aorta and pulmonary artery measured by Doppler echocardiography in the midtrimester normal human fetus

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SUMMARY The time to peak velocity was measured by Doppler echocardiography in the pulmonary artery in 102 normal human fetuses (gestational age 16–30 weeks). Time to peak velocity in the aorta was measured in 72. In 58 both measurements could be made in the same fetus. The time to peak velocity was shorter in the pulmonary artery than in the aorta. This difference was statistically significant. This suggests that in the midtrimester fetus mean pressure in the pulmonary artery is higher than in the aorta.

Cross sectional echocardiographic examination of the normal fetal heart has become well established in recent years.[1-3] The intracardiac structures can be readily identified and the Doppler sample volume accurately positioned to allow the characteristics of the blood flow velocity waveform through each cardiac valve to be evaluated.[4]

The prediction of pulmonary artery pressure by non-invasive methods in children and adults has been reported recently. Studies using Doppler echocardiography in pulmonary hypertension have shown a good correlation between the acceleration time and the mean pressure measured by cardiac catheterisation.[5 6] As pulmonary artery pressure increased the time from the onset of ejection to peak velocity became shorter.

We compared the acceleration time in the pulmonary artery and aorta in a series of normal fetuses to assess the relative mean arterial pressures in fetal life.

Patients and methods

One hundred and two pregnant women were selected for fetal echocardiographic examination between 16 and 30 weeks' gestation. The study group were referred to us because of a previous family history of congenital heart disease or they came as volunteers from the routine antenatal clinic. All the fetuses were examined by a Hewlett-Packard 722020A phased array sector scanner with a 5 MHz transducer. The fetal heart was first examined by cross sectional echocardiography to establish that its structure was normal. Those with any abnormality of pregnancy or of the fetal heart were excluded. Singleton pregnancies only were examined. Gestational age was estimated from the fetal biparietal diameter and the femoral length or both. The pulmonary artery or the aorta was imaged in a suitable

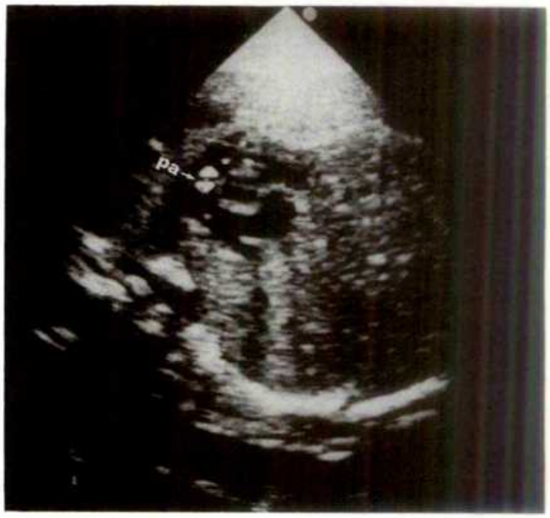

Fig 1 *The Doppler sample volume is positioned in the main pulmonary artery just distal to the valve leaflets. Note that the angle of interrogation is very close to the direction of blood flow.*

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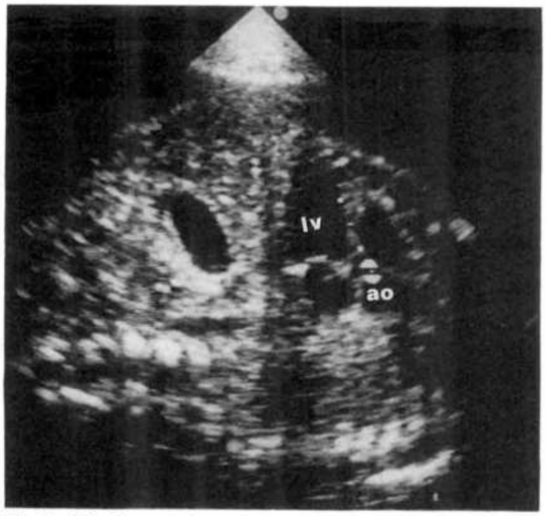

Fig 2 *The heart is imaged in the long axis of the left ventricle (lv). The Doppler sample volume is then placed in the correct orientation for interrogation of the aortic valve. ao, aorta.*

orientation with the Doppler sample volume positioned distal to the valve leaflets. Only those tracings where the direction of the ultrasound beam was < 30° from the direction of blood flow were considered to be acceptable (figs 1 and 2). The blood flow velocity was displayed on the strip chart at paper speed of 100 cm/s and recorded on videotape.

After the examination the measurements were made from the videotape. The measurement was made on screen by positioning one calliper at the onset of ejection and the other at the peak of velocity on a frozen frame tracing from the respective valve (figs 3 and 4). The interval between the callipers was then displayed on the screen. Only clear complexes were used and the acceleration time was the average of 10–20 cardiac cycles.

Results

The time to peak velocity in the pulmonary artery was measured in all 102 patients and aortic measurements were obtained in 72. In 58 fetuses both measurements were made in the same patient. In

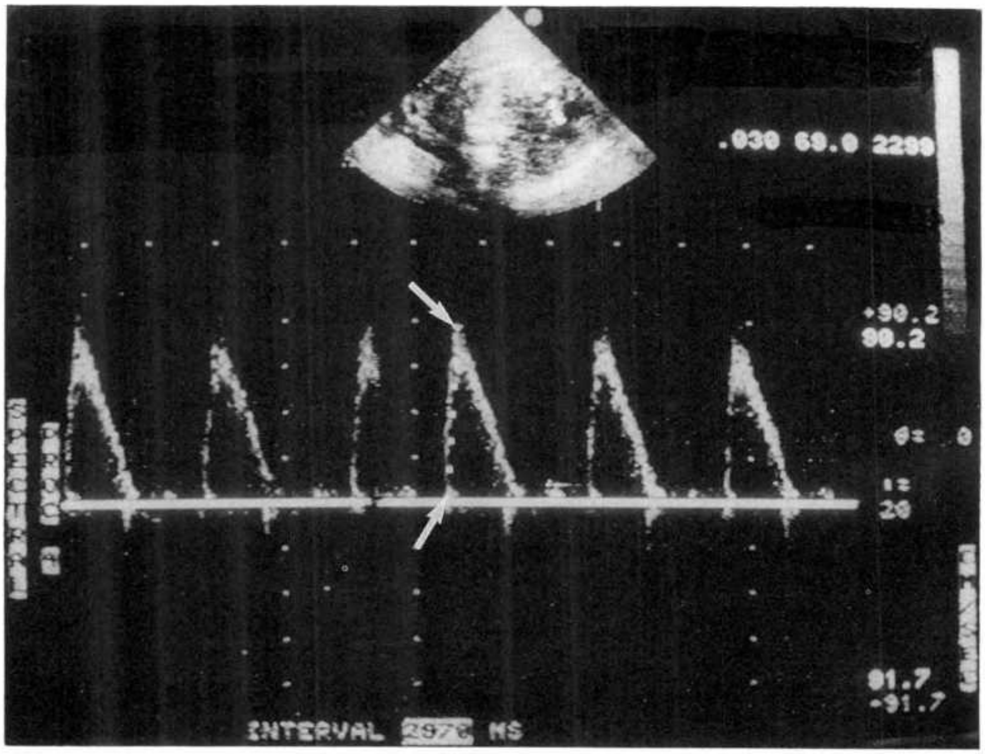

Fig 3 *The blood flow velocity waveform through the pulmonary artery. The callipers are positioned at the onset of ejection and at the peak of velocity. The time between the two measurements is shown on the screen.*

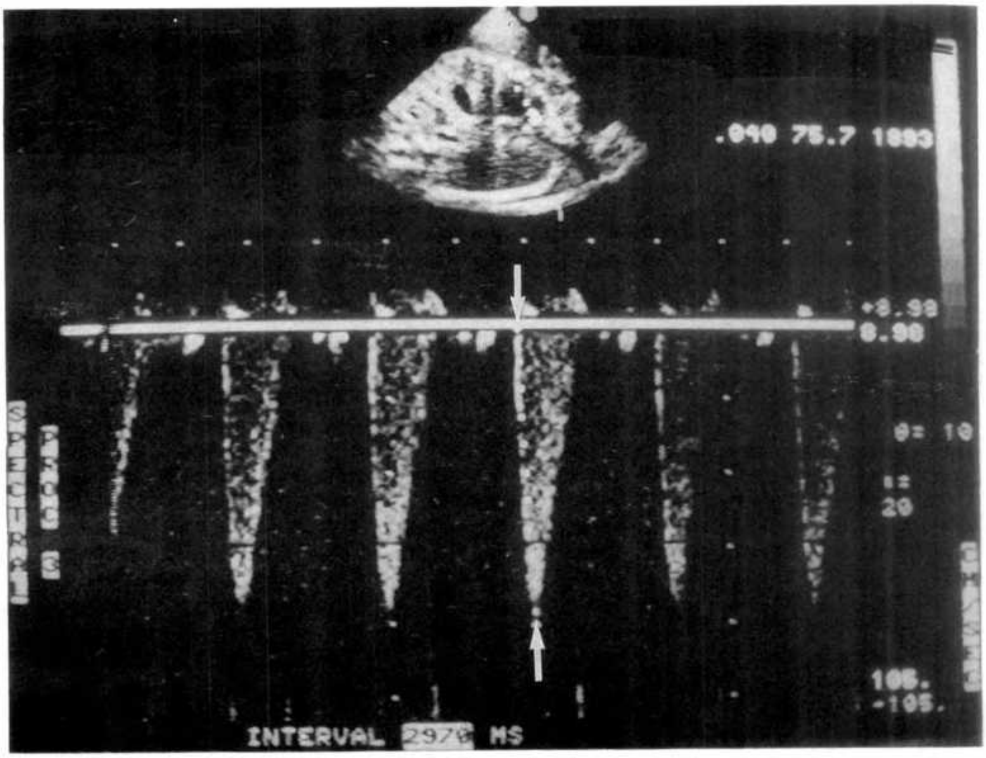

Fig 4 *The blood flow velocity waveform through the aortic valve.*

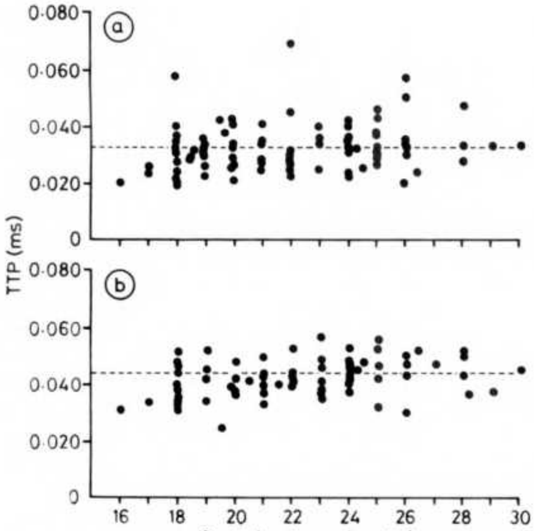

Fig 5 *The time to peak velocities plotted against gestational age for both the pulmonary artery (a) and the aorta (b). There was no association with gestational age. The values for the pulmonary artery (a) vary slightly more than the aortic values (b).*

these 58 we compared the time to peak velocity in the great arteries.

Figures 3 and 4 show that the shape of the velocity tracings was similar in the two arteries. The time to peak velocity was shorter in the pulmonary artery than in the aorta (mean (SD) pulmonary artery 0·0321s (0·0085), vs mean (SD) aorta 0·0437s (0·0088)) ($p = < 0·0000001$ by an unpaired *t* test). There was no detectable change with gestational age in the time to peak velocity in either of the great arteries (fig 5).

Discussion

Fewer measurements of aortic velocity were obtained because at the start of the study we found it more difficult to achieve a small angle between the direction of the beam and the direction of flow in this vessel. Later in the study measurements in both the aorta and pulmonary artery were readily achieved in the correct orientation.

Kitabatake *et al* described the close correlation between pulmonary artery pressure and time to peak velocity in 33 adult patients studied by Doppler and cardiac catheterisation.[5] These results were confirmed by Serwer *et al* in a study of 33 children[6] and by Kosturakis *et al* in a study of 17 children with structural heart disease undergoing cardiac catheterisation.[7]

On the basis of these studies we expect that fetal results will also reflect the relative mean arterial pressures found prenatally. Our results suggest that between 16–30 weeks' gestation the mean pressure in the pulmonary artery is higher than that in the aorta and that this reflects a difference in resistance between the two circuits.

Thus when there is a restrictive ventricular septal defect in a fetus there may be a right to left shunt. Because the pressure difference between the two sides of the heart is probably small, however, the shunt is not expected to be large. We have been unable to detect shunting in prenatal life through a ventricular septal defect by direct Doppler interrogation. Some workers who have had the opportunity to examine such cases with colour Doppler have suggested that there is a left to right shunt.[8] This does not accord with our findings.

It is perhaps surprising that there was no detectable change in pulmonary artery time to peak velocity estimations with increasing gestation. Placental resistance is known to fall as pregnancy advances[9 10] and this might be expected to affect the results of time to peak estimation in the pulmonary artery.

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References

1 Lange LW, Sahn DJ, Allen HD, Goldberg SJ, Anderson C, Giles H. Qualitative real-time cross-sectional echocardiographic imaging of the human fetus during the second half of pregnancy. *Circulation* 1980;62.799–806

2 Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS. Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. *Pediatrics* 1980;65:1059–66.

3 Allan LD, Tynan MJ, Campbell S, Wilkinson JL, Anderson RH. Echocardiographic and anatomical correlates in the fetus. *Br Heart J* 1980;44:445–51.

4 Allan LD, Chita SK, Al-Ghazali W, Crawford DC, Tynan M. Doppler echocardiographic evaluation of the normal human fetal heart. *Br Heart J* 1987;57:528–33.

5 Kitabatake A, Inoue M, Asao M, *et al*. Non-invasive evaluation of pulmonary hypertension by pulsed Doppler technique. *Circulation* 1983;68:302–9.

6 Serwer GA, Cougle AG, Eckerd JM, Armstrong BE. Factors affecting use of the Doppler-determined time from flow onset to maximal pulmonary artery velocity for measurement of pulmonary artery pressure in children. *Am J Cardiol* 1986;58:352–6.

7 Kosturakis D, Goldberg SJ, Allen HD, Loeber C. Doppler echocardiographic prediction of pulmonary hypertension in congenital heart disease. *Am J Cardiol* 1984;53:1110–5.

8 Sahn DJ, Hagen-Ansert S. Echo Doppler color flow mapping studies for the elucidation of cardiovascular anatomy and physiology in the human fetus [Abstract]. *J Am Coll Cardiol* 1986;7(2):37A.

9 Trudinger B, Warwick W, Giles WB, Cook CM, Bombardier J, Collins L. Fetal umbilical artery flow velocity waveform and placental resistance: clinical significance. *Br J Obstet Gynaecol* 1985;92:23–30.

10 Giles WB, Trudinger B, Baird PJ. Fetal umbilical artery waveform and placental resistance: pathological correlation. *Br J Obstet Gynaecol* 1985;92:31–8.

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To what extent does the size of a ventricular septal defect correlate with haemodynamic data derived from cardiac catheterisation?

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SUMMARY A simplified model based on Gorlin's formula was used to derive an index of the cross sectional area of ventricular septal defects from commonly used cardiac catheterisation data. This index was compared with the area of the defect measured during operation and expressed as a ratio to the cross sectional area of the aorta. The highly significant linear relation ($r = 0.94$) between this index of the defect area and the size of the defect measured at operation means that the severity of a ventricular septal defect can be assessed from haemodynamic data obtained at cardiac catheterisation.

It is generally accepted that in patients with a ventricular septal defect the size of the defect is the most important factor determining the clinical picture and haemodynamic function[1 2]; however, little is known about how the size of the defect affects haemodynamic function. The Gorlin formula describes the relation between the shunt flow and the pressure gradient across the defect by a theorem of orifice flow.[3] Because the formula does not take account of the properties of the vascular systems it cannot give a complete picture of the haemodynamic function. We have expanded Gorlin's approach and have developed a theoretical model to determine the basic relation between haemodynamic function and the anatomical size of ventricular septal defect.

Patients and methods

STUDY GROUPS

We studied 46 of the 66 children with isolated ventricular septal defect who had defects closed at Fukuoka Children's Hospital Medical Centre from October 1980 to November 1984. We had cardiac catheterisation data, cineangiogram records, and records obtained at operation for these cases. Age at operation ranged from three months to 13 years (median 11 months). The interval from cardiac catheterisation to operation ranged from one day to seven months (median 10 days). According to Kirklin *et al*'s anatomical classification of ventricular septal defects[4] there were 13 type I cases, 31 type II cases, and two type I + II.

MODEL FOR ANALYSIS OF VENTRICULAR SEPTAL DEFECT

An exact description of the haemodynamics of a ventricular septal defect based on fluid dynamics is difficult to devise and may not be practical to apply. We therefore used a simplified model to analyse the haemodynamics of the defect from the commonly used cardiac catheterisation data. This model assumes the following: (*a*) that pressures in the right and left ventricles and flow rates through the aorta, the pulmonary artery, and the defect are constant during systole; (*b*) that shunt flow through the defect only occurs from left to right; (*c*) that left ventricular systolic pressure (P_{LV}) and right ventricular systolic pressure (P_{RV}) are equal to their peak systolic pressures; (*d*) that throughout the cardiac cycle pressures in both the systemic and pulmonary

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Table *Anatomical measurement and cardiac catheterisation data in 46 patients with ventricular septal defect*

			Anatomical measurement			*Cardiac catheterisation*			
Case No	*Age*	*VSD type**	*VSD dimension (mm × mm)†*	*Ao diameter (mm)*	*PA diameter (mm)*	$Q_p{:}Q_s$	$P_{RV}{:}P_{LV}$	$R_p{:}R_s$	$\bar{P}_s{:}P_{LV}$
1	1 yr 2 mnth	I	8 × 6	11·4	15·2	2·50	0·35	0·09	0·74
2	9 mnth	II	10 × 10	11·4	18·9	3·06	0·90	0·27	0·75
3	6 mnth	II	10 × 10	11·1	15·1	2·08	0·98	0·53	0·67
4	1 yr 11 mnth	I	5 × 3	12·6	16·6	1·68	0·45	0·23	0·70
5	2 yr 4 mnth	I	5 × 4	16·3	21·7	1·53	0·42	0·20	0·78
6	8 mnth	I	10 × 9	10·8	18·3	3·30	0·56	0·14	0·77
7	5 yr 7 mnth	I	5 × 5	16·7	24·4	1·55	0·34	0·17	0·79
8	12 yr 10 mnth	I	3 × 3	23·8	28·1	1·20	0·21	0·14	0·79
9	9 mnth	II	8 × 8	11·0	19·6	2·47	0·84	0·34	0·73
10	10 mnth	II	7 × 7	11·0	17·5	2·05	0·78	0·40	0·71
11	10 mnth	I + II	10 × 10	13·3	20·6	2·14	0·88	0·46	0·70
12	2 yr 0 mnth	II	7 × 7	12·5	19·2	2·37	0·45	0·17	0·81
13	7 mnth	II	5 × 5	9·8	12·0	2·10	0·49	0·23	0·67
14	11 mnth	I	10 × 10	9·3	24·1	3·63	0·81	0·22	0·72
15	11 mnth	II	7 × 7	13·2	18·9	1·94	0·59	0·24	0·72
16	7 mnth	II	8 × 8	11·5	19·5	2·42	0·88	0·34	0·74
17	10 mnth	II	5 × 5	11·2	14·8	2·05	0·51	0·17	0·73
18	3 mnth	II	10 × 10	8·1	11·1	1·85	0·99	0·58	0·62
19	5 mnth	II	6 × 6	11·1	16·3	2·32	0·72	0·26	0·77
20	7 yr 10 mnth	I	3 × 3	17·8	21·6	1·20	0·24	0·14	0·86
21	6 yr 6 mnth	II	16 × 15	19·0	26·6	1·66	0·99	0·57	0·84
22	7 yr 3 mnth	II	8 × 8	16·0	21·5	1·75	0·64	0·46	0·55
23	4 yr 5 mnth	II	10 × 10	16·0	23·7	2·30	0·38	0·09	0·67
24	1 yr 3 mnth	I + II	12 × 12	12·9	17·6	3·47	0·82	0·21	0·69
25	5 mnth	II	8 × 8	10·2	16·7	2·59	0·92	0·30	0·76
26	5 mnth	I	9 × 9	10·4	16·7	2·04	0·99	0·46	0·69
27	1 yr 6 mnth	II	14 × 13	11·8	23·3	1·62	0·99	0·76	0·65
28	1 yr 3 mnth	I	4 × 4	13·5	17·7	1·80	0·41	0·17	0·71
29	11 mnth	II	12 × 8	10·0	15·4	2·76	0·90	0·33	0·71
30	11 mnth	II	7 × 7	11·6	19·3	2·25	0·54	0·16	0·67
31	7 mnth	II	10 × 8	10·0	18·2	2·40	0·97	0·36	0·71
32	1 yr 0 mnth	II	9 × 8	13·0	20·8	2·29	0·81	0·33	0·76
33	1 yr 0 mnth	II	12 × 12	10·7	20·2	2·96	0·97	0·29	0·90
34	7 yr 5 mnth	I	3 × 3	14·8	16·4	1·18	0·26	0·13	0·87
35	8 mnth	II	8 × 8	11·5	16·5	2·58	0·69	0·25	0·70
36	5 mnth	II	10 × 10	10·0	14·4	2·66	0·97	0·33	0·73
37	1 yr 5 mnth	II	7 × 7	12·2	18·3	2·18	0·56	0·22	0·59
38	1 yr 0 mnth	II	7 × 7	12·2	17·0	2·30	0·44	0·14	0·72
39	4 mnth	II	9 × 9	9·6	15·5	3·10	0·82	0·23	0·72
40	11 mnth	II	8 × 8	9·8	13·1	2·97	0·77	0·19	0·70
41	1 yr 1 mnth	II	8 × 8	14·0	17·8	2·36	0·68	0·25	0·68
42	10 mnth	II	6 × 6	11·1	15·5	2·54	0·49	0·15	0·65
43	6 yr 6 mnth	II	16 × 14	16·8	20·8	3·06	0·91	0·24	0·89
44	4 mnth	I	8 × 5	9·6	18·3	2·83	0·56	0·18	0·74
45	4 mnth	II	8 × 8	9·3	14·1	3·10	0·84	0·25	0·66
46	3 yr 4 mnth	I	7 × 7	13·7	21·1	1·96	0·38	0·21	0·70

*Kirklin's anatomical classification.[4]

†Long diameter × short diameter.

VSD, ventricular septal defect; Ao, aortic; PA, pulmonary arterial, $Q_p{:}Q_s$, ratio of pulmonary blood flow to systemic blood flow; $P_{RV}{:}P_{LV}$, ratio of right ventricular to left ventricular peak systolic pressure; $R_p{:}R_s$, ratio of pulmonary vascular resistance to systemic vascular resistance, $\bar{P}_s{:}P_{LV}$, ratio of mean systemic to left ventricular peak systolic pressure.

arterial systems are constant and equal to mean vascular pressures ($\bar{P}_s$ and $\bar{P}_p$); (*e*) that flow rates of blood through the defect, the aorta, and the pulmonary artery are proportional to the cross sectional area × $\sqrt{\text{pressure gradient}}$ (Gorlin's formula.[3,5])

An index of the cross sectional area of the defect ($A_{VSD\ index}$) is defined by the following equation:

$$A_{VSD\ index} = (Q_p : Q_s - 1) \times \sqrt{(1 - \bar{P}_s : P_{LV})/(1 - P_{RV} : P_{LV})}\ ,$$

where Q_p and Q_s are mean pulmonary and systemic flow respectively, and the index is proportional to the ratio of cross sectional area of the defect to that of the aorta ($A_{VSD}{:}A_{Ao}$), as shown in Appendix equations 9–11. To examine this predicted relation, we compared the index of the area of the defect ($A_{VSD\ index}$) derived from cardiac catheterisation data with the ratio of cross sectional area of the defect to that of the aorta ($A_{VSD}{:}A_{Ao}$) derived from anatomical measurements.

CARDIAC CATHETERISATION

Cardiac catheterisation studies were performed during spontaneous respiration in room air after premedication, usually with 0·1 mg/kg of estazolam or

80 mg/kg of triclofos given orally. Pressures were measured by fluid filled catheters connected to CTC CP-01 transducers. The ratios of right ventricular to left ventricular peak systolic pressure ($P_{RV}:P_{LV}$) and of mean systemic to peak left ventricular pressure ($\bar{P}_s:P_{LV}$) were calculated. When the left ventricular pressure (P_{LV}) was not measured, peak systemic pressure (P_s) was used. The pulmonary to systemic blood flow ratio ($Q_p:Q_s$) and the pulmonary to systemic vascular resistance ratio ($R_p:R_s$) were calculated by the Fick method. The oxygen saturation of haemoglobin was measured by spectrophotometer. Oxygen saturation was used instead of oxygen content to calculate $Q_p:Q_s$, and the content of dissolved oxygen was ignored. The oxygen saturation of mixed venous blood was measured in blood samples from the superior vena cava and the inferior vena cava with the ratio of 3 to 1.[6] The oxygen saturation of pulmonary arterial blood was measured as the average of samples from both pulmonary arterial branches or in one of them; oxygen saturation of systemic arterial blood was measured in samples from the femoral artery or the aorta. Because the blood of the pulmonary vein could not be sampled in most cases, the oxygen saturation was assumed to be the same as that of systemic arterial blood, ignoring the right to left shunt. Because left atrial pressure or pulmonary capillary wedge pressure was not always available we used total pulmonary vascular resistance. The index of defect area ($A_{VSD\ index}$) was calculated from these data.

MEASUREMENTS OF CROSS SECTIONAL AREA

The diameters of the aorta and the pulmonary artery were measured at the level of the valve ring on lateral view cineangiograms. At angiography the aortic valve ring was located near the centre of the lateral image screen and had a diameter of 250 mm. The distance between the *x* ray tube and the image screen was fixed at 900 mm, and the object was placed approximately 200 mm from the image screen. We placed a screen with a lead grid in parallel with the lateral image screen at the midpoint of the aortic valve ring to measure the dimensions of the aorta and the pulmonary artery. As a guide we used the anteroposterior angiogram recorded by video tape. The cross sectional areas of the aorta (A_{Ao}) and of the pulmonary artery (A_{PA}) were calculated from the following formula, assuming a circular cross sectional contour: area $= 1/4 \times \pi \times D^2$, where D was defined as the mean value of maximum and minimum diameter during one cardiac cycle. Since the size of the defect in the beating heart cannot be determined exactly, we measured the size in the arrested heart with sterile callipers during operation. We assumed that the size of the defect in the beating heart had the same relation with that in the arrested heart. The long and short diameters (D_L and D_S) were measured and the cross sectional area (A_{VSD}) was calculated, assuming that the defect was ellipsoidal, by means of the following formula: $A_{VSD} = 1/4 \times \pi \times D_L \times D_S$.

Results

The table shows the anatomical measurements and cardiac catheterisation data in 46 patients. The figure shows the relation between the index of the area of the defect ($A_{VSD\ index}$) and the measured defect area expressed as a ratio to the aortic area ($A_{VSD}:A_{Ao}$). The linear regression equation was:

$$A_{VSD}:A_{Ao} = 0{\cdot}28 \times A_{VSD\ index} + 0{\cdot}02$$
$$(r = 0{\cdot}94, n = 46, p < 0{\cdot}001).$$

The highly significantly linear relation between $A_{VSD\ index}$ and $A_{VSD}:A_{Ao}$ and the negligible y axis intercept indicates that the index of the area of the defect derived from cardiac catheterisation data is proportional to the ratio of the area of the defect to the aortic area.

Discussion

The model we proposed for the assessment of the haemodynamic function of a ventricular septal defect is simple but its application depends on various assumptions. Our results show a basic relation

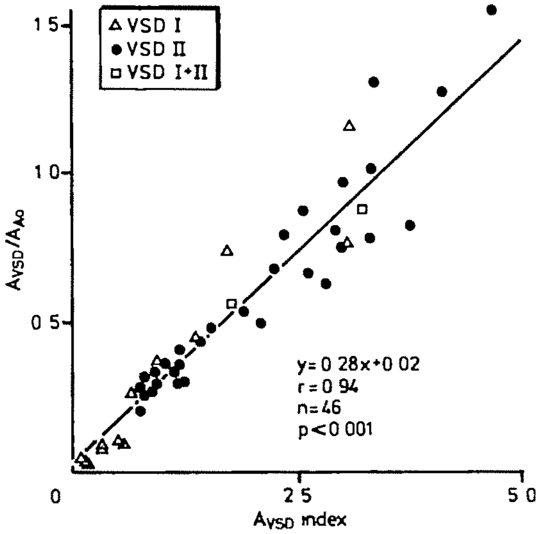

Figure *Correlation between the index of cross sectional area of the defect ($A_{VSD\ index}$) derived from the cardiac catheterisation data and the ratio of cross sectional area of the defect to that of the aorta ($A_{VSD}:A_{Ao}$) derived from the anatomical measurements.*

P, 25, 733.

between haemodynamic function and the anatomy of the defect; they also suggest that it is important to standardise the size of the defect according to cross sectional area of the aorta rather than to use the defect size itself.

Cardiac catheterisation is used to evaluate the severity of ventricular septal defect and to determine indications for operation. Usually three haemodynamic indices (that is pulmonary to systemic blood flow ratio ($Q_p:Q_s$), pulmonary to systemic systolic pressure ratio ($P_p:P_s$), and pulmonary to systemic vascular resistance ratio ($R_p:R_s$)) are used for such assessment.[7 8] The fact that these variables are not mutually independent sometimes makes it difficult to evaluate the severity of the defect from cardiac catheterisation data. We think that a reasonable assessment can be made by using two independent indices. That is the index of defect area ($A_{VSD\ index}$), which represents the size of the defect, and the ratio of pulmonary vascular resistance to systemic vascular resistance ($R_p:R_s$), which represents the vascular property. Apart from six children with a type I ventricular septal defect who were treated to prevent aortic regurgitation caused by prolapse of the aortic cusp, all the others, whose surgical indications were determined mainly from the usual criteria (that is $Q_p:Q_s > 2$ or $P_p:P_s > 0{\cdot}5$), had indices for the area of the defect of > 0·75 and ratios of defect area to aortic area of >0·2. We therefore consider that surgical intervention is not imperative in patients in whom the index of area of the defect is < 0·75, except when they have a type I ventricular septal defect. This criterion for operation corresponds to a defect to aortic diameter ratio of about 0·5 in the case of a round defect.

Equations 12 and 13 in the appendix show that our model also allows estimation of the commonly used haemodynamic indices (that is the ratio of pulmonary to systemic blood flow ($Q_p:Q_s$) and the ratio of right ventricular to left ventricular peak systolic pressure ($P_{RV}:P_{LV}$)) from the two anatomical values (that is the ratio of the defect area to the aortic area ($A_{VSD}:A_{Ao}$) and the ratio of the pulmonary arterial area to the aortic area ($A_{PA}:A_{Ao}$)) and the two vascular indices (that is the ratio of pulmonary vascular resistance to systemic vascular resistance ($R_p:R_s$) and the ratio of mean systemic pressure to systolic systemic pressure ($\bar{P}_s:P_s$)). There was a linear relation between the haemodynamic indices estimated from the model ($Q_p:Q_{s\ est}$ and $P_{RV}:P_{LV\ est}$) and those derived directly from cardiac catheterisation ($Q_p:Q_{s\ cath}$ and $P_{RV}:P_{LV\ cath}$). The linear regression equations were:

$$Q_p:Q_{s\ cath} = 0{\cdot}93 \times Q_p:Q_{s\ est} + 0{\cdot}20 \qquad (r = 0{\cdot}92,\ n = 46),$$

and

$$P_{RV}:P_{LV\ cath} = 1{\cdot}05 \times P_{RV}:P_{LV\ est} - 0{\cdot}08 \qquad (r = 0\ 94,\ n = 46),$$

respectively. These results indicate the usefulness of this model and suggest that the haemodynamic features of ventricular septal defect are determined mainly by anatomical values (that is $A_{VSD}:A_{Ao}$ and $A_{PA}:A_{Ao}$) and the vascular properties (that is $R_p:R_s$ and $\bar{P}_s:P_s$).

In conclusion, the index of cross sectional area of the defect, deduced from our model, links haemodynamic function with anatomy. That is, this index of area of the defect, calculated from the cardiac catheterisation data, correlates well with the area of the defect expressed as a ratio to the aortic area. This index may be used to grade the severity of the disease. We are now applying this method to the estimation of haemodynamic function from echocardiographic measurements.

Appendix

MODEL OF VENTRICULAR SEPTAL DEFECT

Adopting the assumptions described above, we constructed a model of ventricular septal defect. According to the Gorlin formula, flow rates through the aorta (F_{Ao}), through the pulmonary artery (F_{PA}), and through the defect (F_{VSD}) during systole are expressed as:

$$F_{Ao} = \alpha_1 \times A_{Ao} \times \sqrt{(P_{LV} - \bar{P}_s)} \qquad (1)$$

$$F_{PA} = \alpha_2 \times A_{PA} \times \sqrt{(P_{RV} - \bar{P}_p)} \qquad (2)$$

$$\text{and } F_{VSD} = \beta \times A_{VSD} \times \sqrt{(P_{LV} - P_{RV})}, \qquad (3)$$

where the empirical coefficients for F_{Ao}, F_{PA}, and F_{VSD} are α_1, α_2, and β respectively; and A_{Ao}, A_{PA}, and A_{VSD} are the cross sectional area of the aorta, pulmonary artery, and septal defect respectively.

F_{PA} is the sum of F_{Ao} and F_{VSD} as

$$F_{PA} = F_{Ao} + F_{VSD}. \qquad (4)$$

Systemic vascular resistance (R_s) and pulmonary vascular resistance (R_p) are determined as

$$R_s = \bar{P}_s / Q_s \qquad (5)$$

$$\text{and } R_p = \bar{P}_p / Q_p, \qquad (6)$$

where Q_s and Q_p are mean systemic flow and mean pulmonary flow.

The relation between F_{Ao} and Q_s, and F_{PA} and Q_p can be described as

$$F_{Ao} = Q_s \times (T/T_s) \qquad (7)$$

$$\text{and } F_{PA} = Q_p \times (T/T_s), \qquad (8)$$

where T and T_s are the duration of one cardiac cycle and of systolic interval.

From the above simultaneous equations (1)-(8), the following equation can be deduced as

$$A_{VSD}:A_{Ao} = (\alpha_1/\beta) \times (Q_p:Q_s - 1) \times \sqrt{(1 - \bar{P}_s:P_{LV})/(1 - P_{RV}:P_{LV})}. \quad (9)$$

Here index of cross sectional area of the defect ($A_{VSD\ index}$) is defined as

$$A_{VSD\ index} = (Q_p:Q_s - 1) \times \sqrt{(1 - \bar{P}_s:P_{LV})/(1 - P_{RV}:P_{LV})}. \quad (10)$$

Substituting $A_{VSD\ index}$, equation (9) can be rewritten as

$$A_{VSD}:A_{Ao} = (\alpha_1/\beta) \times A_{VSD\ index}, \quad (11)$$

which indicates the proportional relation between $A_{VSD\ index}$ and A_{VSD}:A_{Ao}.

The second degree equation for Q_p:Q_s also can be deduced from the above equations as:

$$[(A_{PA}:A_{Ao})^2 + (A_{VSD\ index})^2] \times (Q_p:Q_s)^2 + [\gamma \times (A_{VSD\ index})^2 \times (R_p:R_s) - 2] \times (A_{PA}:A_{Ao})^2 \times (Q_p:Q_s) + [1 - (1 + \gamma) \times (A_{VSD\ index})^2] \times (A_{PA}:A_{Ao})^2 = 0, \quad (12)$$

where the empirical coefficients α_1 and α_2 are assumed to be the same, and γ is defined as $\gamma = 1/[(P_{LV}:\bar{P}_s) - 1]$.

Similarly $P_{RV}:P_{LV}$ can be deduced as

$$P_{RV}:P_{LV} = [(1/\gamma) \times (A_{Ao}:A_{PA})^2 \times (Q_p:Q_s)^2 + (R_p:R_s) \times (Q_p:Q_s)] \times (\bar{P}_s:P_{LV}). \quad (13)$$

$\bar{P}_s:P_s$ was used instead of $\bar{P}_s:P_{LV}$ in the calculation.

We thank Dr Kenji Sunagawa for discussion and Mariko Ohara for comments.

References

1 Selzer A. Defect of the ventricular septum. *Arch Intern Med* 1949;84:798–825.

2 Damman JF, Thompson WM, Sosa O, Christlieb I. Anatomy, physiology and natural history of simple ventricular septal defects. *Am J Cardiol* 1960;5:136–66.

3 Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valve, and central circulatory shunts. I. *Am Heart J* 1951;41:1–29.

4 Kirklin JW, Harshbarger HG, Donald DE, Edwards JE. Surgical correction of ventricular septal defect: anatomic and technical considerations. *J Thorac Surg* 1975;33:45–59.

5 Milnor WR. *Hemodynamics*. Baltimore: Williams and Wilkins, 1982:23–4.

6 Yang SS, Bentivoglio L, Maranhao V, Goldberg H. *From cardiac catheterization data to hemodynamic parameters*. Philadelphia: FA Davis, 1978:211.

7 McNamara DG. Medical problems in correction of ventricular septal defects. *Prog Cardiovasc Dis* 1965;8:44–59.

8 Cartmill TB, DuShane JW, McGoon DC, Kirklin JW. Results of repair of ventricular septal defect. *J Thorac Cardiovasc Surg* 1966;52:486–501.

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Secretion of atrial natriuretic peptide from the heart in man

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SUMMARY Plasma concentrations of atrial natriuretic peptide were measured in eight patients undergoing elective cardiac catheterisation and angiography. All patients had normal resting pressures in the cardiac chambers and no clinical evidence of heart failure. Plasma atrial natriuretic peptide rose significantly from the superior vena cava into the right atrium and right ventricle. The increase into the right atrium was variable, with no increase in three subjects, but there was a consistent increase in all subjects from the superior vena cava to the right ventricle. These findings in the right atrium are probably caused by inadequate mixing and streaming of blood from the coronary sinus containing high concentrations of atrial natriuretic peptide. There was no increase in the concentration of natriuretic peptide from the pulmonary artery to the left ventricle, but the concentrations in the left ventricle were significantly higher than in the superior vena cava.

These findings demonstrate that the heart secretes atrial natriuretic peptides in the absence of cardiac failure. Studies based on sampling of the right atrium will not accurately measure cardiac secretion of atrial natriuretic peptide and will therefore be likely to obscure the mechanisms responsible for regulating its secretion. The right ventricle and pulmonary artery are the best sampling sites to measure atrial natriuretic peptide release from the right atrium.

There is increasing evidence that atrial natriuretic peptide may be important in the regulation of salt and water balance.[1] The mechanisms controlling the release of atrial natriuretic peptide are not yet clear. Both in subjects with normal[2] and with raised right atrial pressure,[2,3] plasma concentrations of atrial natriuretic peptide in the right atrium have been reported to correlate significantly with right atrial pressure. However, the plasma concentration of atrial natriuretic peptide in coronary sinus blood is many times higher than that in peripheral venous and right atrial blood.[4–7] Samples of right atrial blood are therefore likely to be of incompletely mixed venous blood. Richards *et al*[5] and Sato *et al*[6] confined their analysis of the mechanisms determining release of atrial natriuretic peptide to studying relations with concentrations of atrial natriuretic peptide in the pulmonary artery and they did not consider changes in plasma concentrations of atrial natriuretic peptide at different cardiac sites within the same individual.

We measured plasma concentrations of atrial natriuretic peptide in blood samples taken from a peripheral vein, the superior vena cava, and in the chambers of the heart during routine cardiac catheterisation and coronary angiography in patients who had possible ischaemic heart disease but normal cardiac pressures.

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Patients and methods

The eight white patients (five men and three women; mean age 60·5 years, range 54–67) studied were undergoing elective cardiac catheterisation as part of routine assessment of known or suspected cardiac disease (ischaemic heart disease seven; aortic stenosis one). Six were on drug treatment (β adrenergic blockers, calcium entry antagonists, nitrates). No patient had overt cardiac failure, and all had normal renal and liver function.

Cardiac catheterisation was performed via the right brachial artery under local anaesthesia with 1% lignocaine. A size 7 French multipurpose catheter (521–776 Cordis Corporation, Miami, USA) was inserted and used to measure pressure and to take blood samples from a peripheral vein, the superior vena cava, right atrium, right ventricle, and pulmonary artery. Patients were given 5000 IU heparin without bacteriocide immediately after the insertion of the arterial catheter (size 8 French National Institute of Health catheter 512–845, Cordis Corporation) that was used to measure arterial and left ventricular pressures and obtain blood samples. We recorded pressures with a semiconductor transducer (Medex Incorporated, Ohio, USA) and fibreoptic system (VR-12, E for M/Honeywell, New York, USA), taking the mid-axillary line as the zero reference point. All recordings and samples were taken with the patients supine before the administration of radiographic dye.

Blood for the measurement of atrial natriuretic peptide was taken into potassium ethylene diamine tetra-acetic acid and trasylol (aprotinin, Bayer, 2000 kIU/10 ml blood) and spun immediately at 4°C. Separated plasma was stored at −20°C. After Sep-pak extraction we measured immunoreactive atrial natriuretic peptide by radioimmunoassay.[8] Plasma renin activity[9] and aldosterone[10] were also measured by radioimmunoassay.

We used the Statistical Package for Social Sciences of the North Western Universities (on the University of London computer) for statistical analysis by paired t test, the binomial test, and Pearson and Spearman's correlation. Results are given as mean (SE).

Results

PLASMA CONCENTRATIONS OF ATRIAL NATRIURETIC PEPTIDE

Plasma concentrations of atrial natriuretic peptide in the right atrium (45·2 (8·6) pg/ml), in the right ventricle (43·8 (7·7) pg/ml) and in the pulmonary artery (43·1 (6·8) pg/ml) were significantly higher than the concentration in the superior vena cava (32·0 (5·4) pg/ml) (fig 1). Examination of individual changes from the superior vena cava into the right heart showed that in three of the eight subjects there was no change into the right atrium (fig 2a), whereas concentrations of atrial natriuretic peptide rose from the superior vena cava to the right ventricle in all eight patients (fig 2b). Plasma concentrations of atrial natriuretic peptide in peripheral vein were not significantly different from those in the superior vena cava. Plasma concentrations of atrial natriuretic peptide in the left ventricle (38·2 (4·5) pg/ml) were significantly greater than those in the superior vena cava (p < 0·05). In contrast with the increase in concentrations across the right side of the heart, concentrations in the left ventricle were not significantly different from those in the pulmonary artery (fig 1). Plasma concentrations of atrial natriuretic peptide were not significantly correlated with right atrial mean or pulmonary capillary wedge pressure. However, plasma concentrations of atrial natriuretic peptide in the right atrium (r = 0·81), right ventricle (r = 0·71), pulmonary artery (r = 0·77), and left ventricle (r = 0·82) correlated significantly with right ventricular systolic pressure (p < 0·05). The significance values quoted for the results are for parametric tests. The non-parametric tests gave similar values.

CALCULATED RATE OF SECRETION OF ATRIAL NATRIURETIC PEPTIDE

There was a mean increase in plasma concentrations of atrial natriuretic peptide of 11·7 pg/ml (95% confidence interval 5·9 to 17·5 pg/ml), from superior vena cava to right ventricle. If the mean stroke volume is estimated to be 80 ml,[11] with a mean heart rate of 60 beats/min during the procedures, then the calculated mean secretion rate for atrial natriuretic peptide across the right atrium in these subjects was approximately 940 pg/s. This assumes adequate mixing of blood by the time it reaches the right ventricle and no appreciable metabolism of atrial

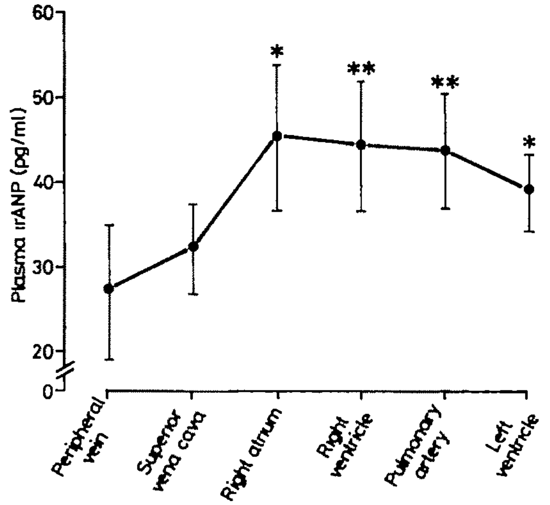


Fig 1 Plasma concentrations of atrial natriuretic peptide in samples from a peripheral vein (n = 6), superior vena cava (n = 8), and heart (n = 8) (*p < 0·05; **p < 0·01 compared with samples from the superior vena cava).

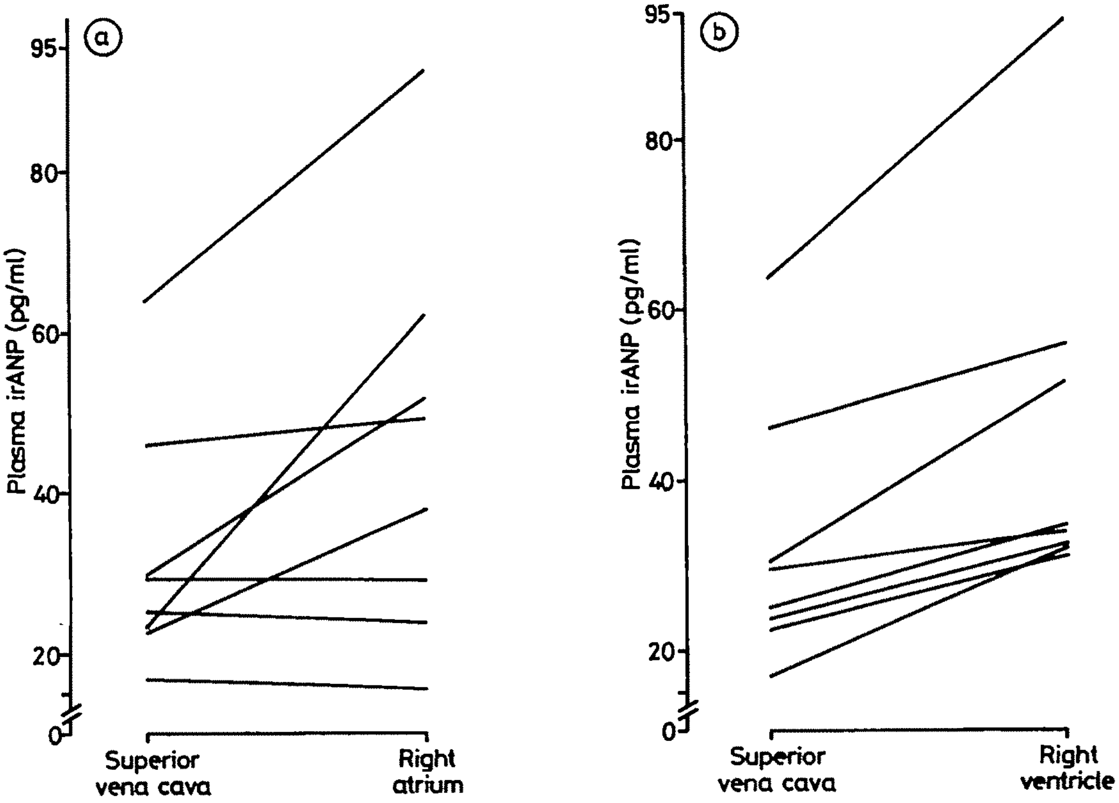


Fig 2 *(a) Plasma concentrations of atrial natriuretic peptide in samples from the superior vena cava and right atrium. (b) Plasma concentrations of atrial natriuretic peptide in samples from the superior vena cava and right ventricle. irANP, immunoreactive atrial natriuretic peptide.*

mixing of blood by the time it reaches the right ventricle and no appreciable metabolism of atrial natriuretic peptide during blood transit between these sampling sites. However, the mean net cardiac secretion of atrial natriuretic peptide calculated from the difference in mean plasma concentrations between the superior vena cava and the left ventricle (6·1 pg/ml (95% confidence interval 1·1 to 11·1 pg/ml) was less, approximately 500 pg/s.

Table 1 *Cardiac catheter pressures in eight patients*

Site	*Pressure (SE) mm Hg*
R atrial mean	1·5 (1·1)
R ventricle systolic	25·0 (1·8)
R ventricle diastolic	1·2 (0·8)
Pulmonary artery systolic	22·0 (0·8)
Pulmonary artery diastolic	7·1 (1·0)
Pulmonary artery mean	11·1 (1·1)
Pulmonary capillary wedge	4·5 (0·9)
L ventricle systolic	130·0 (7·9)
L ventricle diastolic	5·6 (1·2)
L ventricle end diastolic	4·2 (0·6)
Aorta, systolic	120·6 (6·5)
Aorta, diastolic	66·2 (4·1)

CARDIAC PRESSURES

All subjects had normal right atrial mean pressure (range −2 to 6 mm Hg) as well as pulmonary capillary wedge pressure (range 2 to 10 mm Hg) (table 1) and none was hypertensive.

OTHER MEASUREMENTS

All subjects had normal renal and liver function. Plasma renin activity and aldosterone concentrations were within the normal range (table 2).

Table 2 *Analysis of blood from the superior vena cava*

	Mean (SE)
Plasma	
Sodium (mmol/l)	136·5 (2·5)
Potassium (mmol/l)	3·7 (0·1)
Urea (mmol/l)	5·9 (0·6)
Creatinine (µmol/l)	91·4 (10·2)
Calcium (mmol/l)	2·32 (0·09)
Albumin (g/l)	41·6 (1·0)
Haemoglobin (g/dl)	13·6 (0·5)
Packed cell volume (%)	0·40 (0·02)
Plasma renin activity (ng/ml/h)	1·26 (0·65)
Aldosterone (pmol/l)	363·2 (91·1)

Angiography showed normal coronary artery appearances in one patient, coronary artery disease in six, and both coronary artery disease and aortic stenosis in one patient.

Discussion

Our study shows that the concentration of plasma atrial natriuretic peptide increases from the superior vena cava into the right atrium and right ventricle and clearly demonstrates that the heart secretes atrial natriuretic peptide when cardiac pressures are normal. Sugawara *et al* studied four subjects and found a 3–10 fold increase in the concentration of atrial natriuretic peptide in the coronary sinus compared with that in peripheral venous blood.[4] However, the majority of samples were assayed without extraction. This is now known to give erroneously high results because of interference from other substances in the plasma.[7] When cardiac samples from one individual were measured after an extraction procedure no change was found in the plasma concentration of atrial natriuretic peptide from the inferior vena cava to the right atrium or the right ventricle and cardiac pressures were not reported. Direct assay in this individual gave values that were several fold greater than with the extraction procedure.[4]

More recent studies have used an extraction step with either a radioimmunoassay[3 5 6] or a radioreceptor assay[2 12] to study plasma concentrations of atrial natriuretic peptide in subjects undergoing cardiac catheterisation. These have included patients with cardiac failure[2 3 5 6 12] and with normal right atrial pressures.[2 5 6 12] Three of these studies examined correlations between concentrations of atrial natriuretic peptide in the right atrium and other factors.[2 3 12] The other two studies considered the relation between concentrations of atrial natriuretic peptide in the pulmonary artery and cardiac haemodynamic function as well as biochemical measurements. But none of the above studies have examined the changes in plasma concentrations of atrial natriuretic peptide from the periphery across the chambers of the heart within the same individual.

In our study, we considered in detail the changes in plasma concentrations of atrial natriuretic peptide in individual subjects with normal cardiac chamber pressures. We found three of the eight subjects had no increase in plasma atrial natriuretic peptide in the right atrium compared with the superior vena cava, but they did have an increase in the right ventricle. In a further three subjects the rise from the superior vena cava to the right atrium was greater than the rise from the superior vena cava to the right ventricle. The wide variability in changes in concentrations of atrial natriuretic peptide from the superior vena cava to the right atrium in the eight subjects is likely to be due to a combination of the effects of the large contribution of the coronary sinus to atrial natriuretic peptide secretion[4–6] streaming of blood in the right atrium,[13] and within patient variation in the positioning of the sampling catheter in the atrium. The rise in the concentration of atrial natriuretic peptide from the superior vena cava to the right ventricle and the pulmonary artery was very similar in all subjects; mixing of blood containing low concentrations of atrial natriuretic peptide with that containing high concentrations is more likely to have occurred by the time atrial blood has reached these sites. Therefore, studies based on sampling the right atrium[2 3 12] are unlikely to be appropriate for determining the mechanisms of secretion. They may suggest spurious correlations and obscure important factors that determine the release of atrial natriuretic peptide.

Studies of the release of atrial natriuretic peptide from the heart should include sampling of the right ventricle or pulmonary artery or both because this will give a more accurate reflection of atrial secretion than direct right atrial sampling. Although Richards *et al*[5] and Sato *et al*[6] used this approach they gave no evidence to support their contention that the pulmonary artery is the more appropriate sampling site.

There are several possible explanations for the lack of increase in plasma atrial natriuretic peptide from the pulmonary artery to the left ventricle that we found in this study. It may be that the left atrium does not secrete atrial natriuretic peptide. This is unlikely, because, although the concentration of atrial natriuretic peptide in the left atrial muscle is lower, the net amount of atrial natriuretic peptide in the left atrium is similar to that in the right because the mass of the left atrium is greater than that of the right. Inactivation of atrial natriuretic peptide in the pulmonary circulation may possibly be important in man; however, animal studies have failed to show that metabolism of the lungs makes an appreciable contribution to the metabolism of atrial natriuretic peptide.[14] A more likely explanation is that the left atrium secretes atrial natriuretic peptide into the left atrial veins which drain into the coronary sinus and then into the right atrium. The study by Ogawa *et al* supports the idea that release of atrial natriuretic peptide by the left atrium may, at least in cardiac failure, contribute significantly to circulating concentrations because they found a significant correlation between plasma concentrations of atrial natriuretic peptide in a peripheral vein and pulmonary capillary wedge pressure.[15] In our study, in which patients did not have heart failure, at least as judged by the absence of clinical features and by normal resting cardiac pressures, there was no significant correlation between plasma concentrations of atrial natriuretic peptide in the heart and right atrial pressure. However, the right ventricular systolic pressure did correlate significantly with concentrations of atrial natriuretic peptide within all cardiac chambers sampled. The relevance of these findings is not clear and the numbers in our study were too small to allow definite conclusions to be drawn from such correlations.

Calculation of the secretion rate of atrial natriuretic peptide is based on several assumptions, but our study shows it should be possible to calculate approximate secretion of atrial natriuretic peptide across the heart, particularly when cardiac output is measured simultaneously. Our findings indicate that previous reports in which mechanisms for the secretion of atrial natriuretic peptide by the heart were postulated from correlations between haemodynamic and physicochemical variables and concentrations of atrial natriuretic peptide measured in the right atrium should be re-evaluated and the findings confirmed by sampling at sites at which mixing of blood is adequate.

DRJS is a British Heart Foundation Junior Research Fellow. GA MacG is a Wellcome Senior Lecturer.

References

1 Needleman P, Adams SP, Cole BR, *et al.* Atriopeptins as cardiac hormones. *Hypertension* 1985;7:469–82.

2 Raine AEG, Erne P, Burgisser E, *et al.* Atrial natriuretic peptide and atrial pressure in patients with congestive heart failure. *N Engl J Med* 1986;315:533–7.

3 Hartter E, Weissel M, Stummvoll HK, *et al.* Atrial natriuretic peptide concentrations in blood from the right atrium in patient with severe right heart failure *Lancet* 1985;ii:93–4.

4 Sugawara A, Nakao K, Morii N, *et al.* Alpha-human atrial natriuretic polypeptide is released from the heart and circulates *Biochem Biophys Res Commun* 1985;129.439–46.

5 Richards AM, Cleland JGF, Tonolo G, *et al.* Plasma α natriuretic peptide in cardiac impairment. *Br Med J* 1986;293:409–12.

6 Sato F, Kamoi K, Wakiya Y, *et al.* Relationships between plasma atrial natriuretic peptide levels and atrial pressure in man. *J Clin Endocrinol Metab* 1986;63:823–7.

7 Gutkowska J, Bonan R, Roy D, *et al.* Atrial natriuretic factor in human plasma. *Biochem Biophys Res Commun* 1986;139:287–95.

8 Sagnella GA, Markandu ND, Shore AC, MacGregor GA. Effects of changes in dietary salt intake and saline infusion on immunoreactive atrial natriuretic peptide in human plasma. *Lancet* 1985;ii:1208–11.

9 Roulston JE, MacGregor GA. Measurement of plasma renin activity by radioimmunoassay after prolonged cold storage. *Clin Chim Acta* 1978;88.45–8.

10 James VHT, Wilson GA. Determination of aldosterone in biological fluids. In: Reid E, ed. *Assay of drugs and other trace compounds in biological fluids. (Methodological developments in biochemistry.)* Amsterdam: Elsevier, 1976: vol. 5: S149–58.

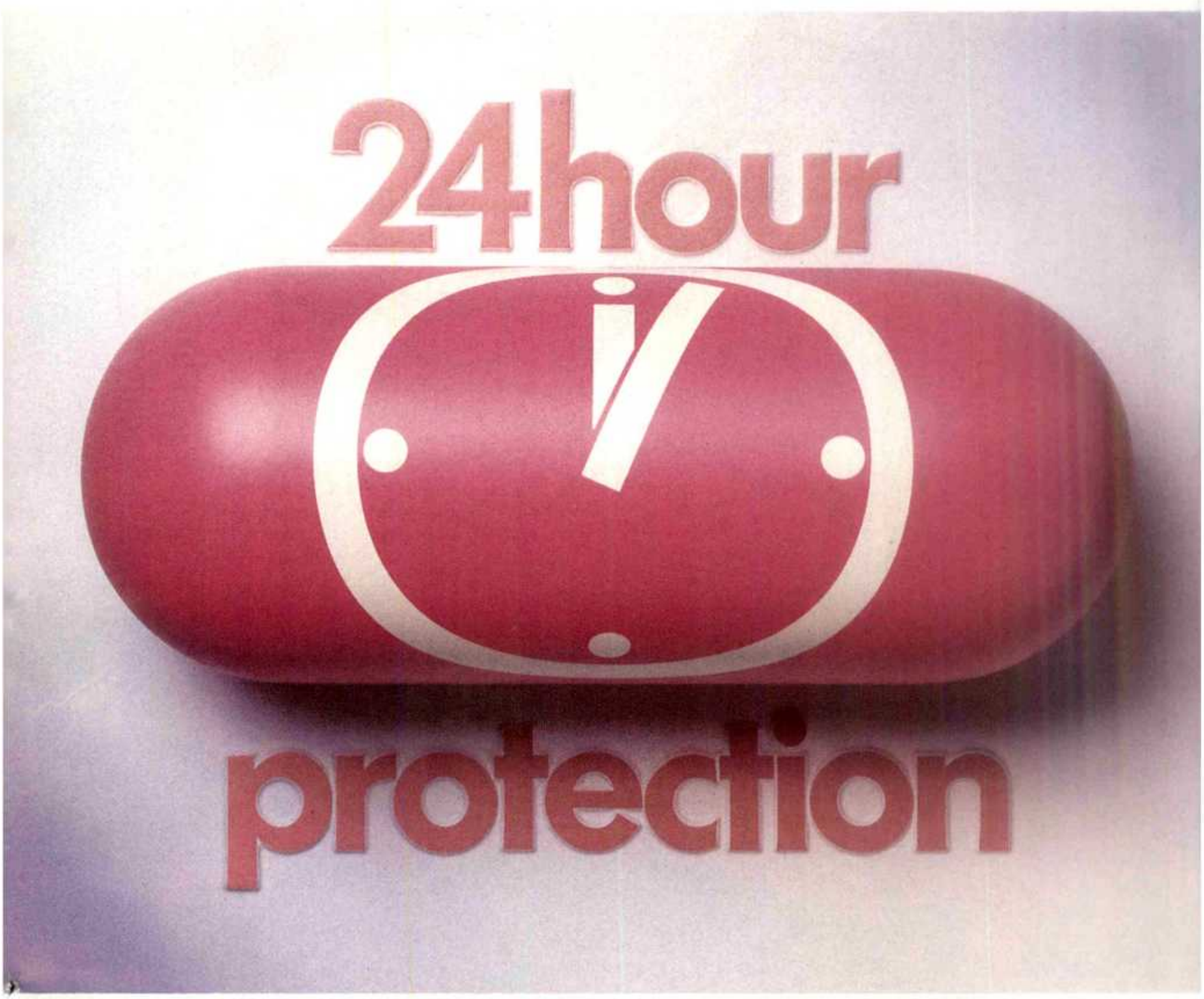
11 Bevegard S, Holmgren A, Jonsson B. The effect of body position on the circulation at rest and during exercise, with special reference to the influence on the stroke volume. *Acta Physiol Scand* 1960;49: 279–98.

12 Burgisser E, Raine AEG, Erne P, Kamber B, Buhler FR. Human cardiac plasma concentrations of atrial natriuretic peptide quantified by radioreceptor assay. *Biochem Biophys Res Commun* 1985;133.1201–9.

13 McDonald DA. *Blood flow in arteries.* 2nd ed. London: Edward Arnold, 1974:87–8.

14 Weselcouch EO, Humphrey WR, Aiken JW. Effect of pulmonary and renal circulations on activity of atrial natriuretic factor. *Am J Physiol* 1985;249:R595–602.

15 Ogawa K, Ito T, Hashimoto H, *et al.* Plasma atrial natriuretic factor in congestive cardiac failure [Letter]. *Lancet* 1986;i:106.



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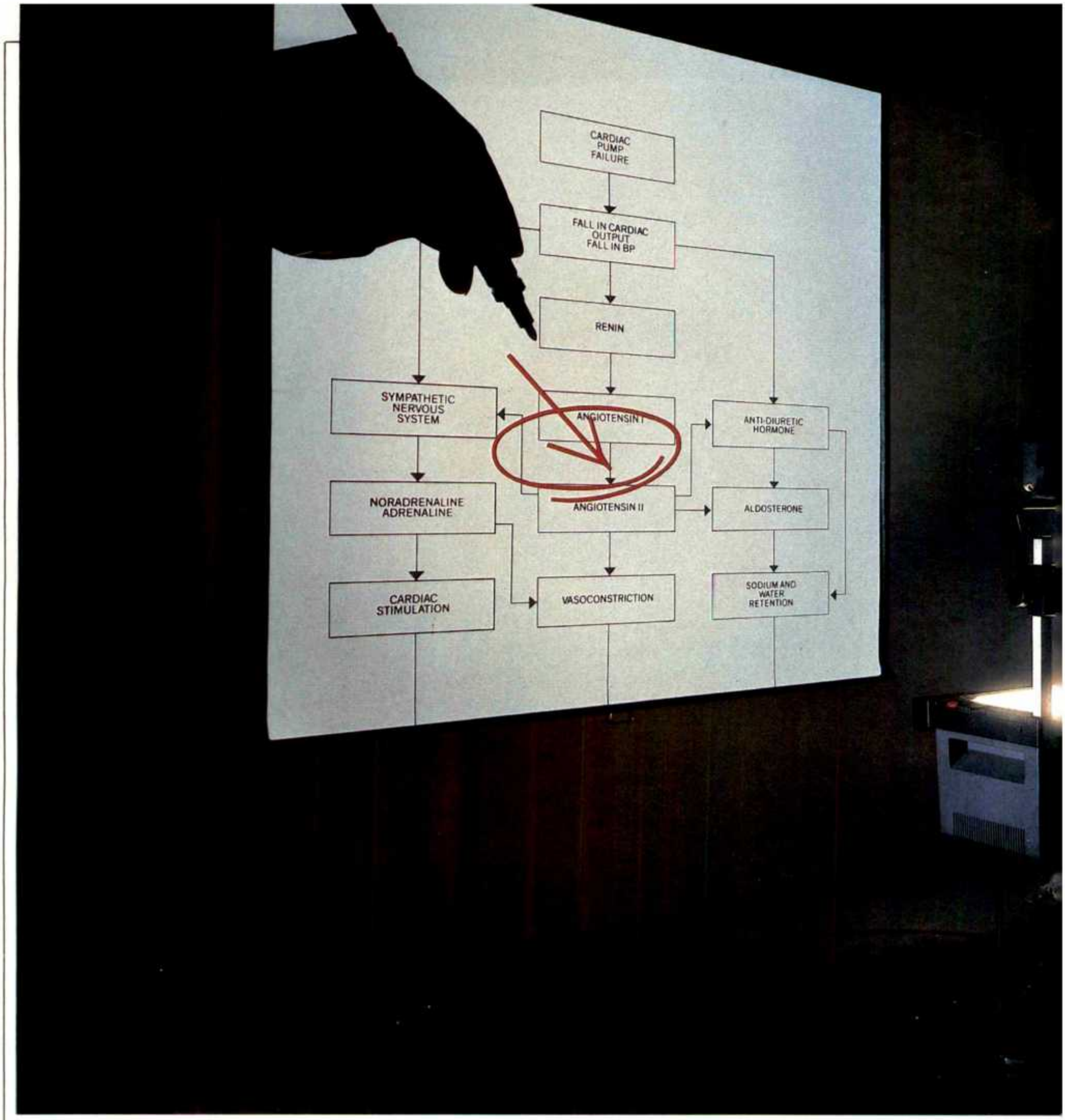

A welcome break in the vicious circle

The so-called *'vicious circle'* in heart failure results from the body's own compensatory mechanisms which act to increase cardiac output and blood pressure. Unfortunately, they may also contribute to a worsening of heart failure by increasing cardiac workload and vasoconstriction.

Central to the *'vicious circle'* is angiotensin II. While conventional therapies, in particular diuretics, relieve one or more of the symptoms of heart failure, they can perpetuate the *'vicious circle'* by stimulating the production of angiotensin II. In contrast 'Innovace' (enalapril maleate, MSD), by blocking the production of angiotensin II, breaks the *'vicious circle'*, resulting in reductions in aldosterone production, stimulation of the sympathetic nervous system and vasoconstriction.

Thus, as an adjunct to diuretic therapy, it is logical to use 'Innovace' to allow long-term improvement in the symptoms of moderate to severe chronic heart failure.

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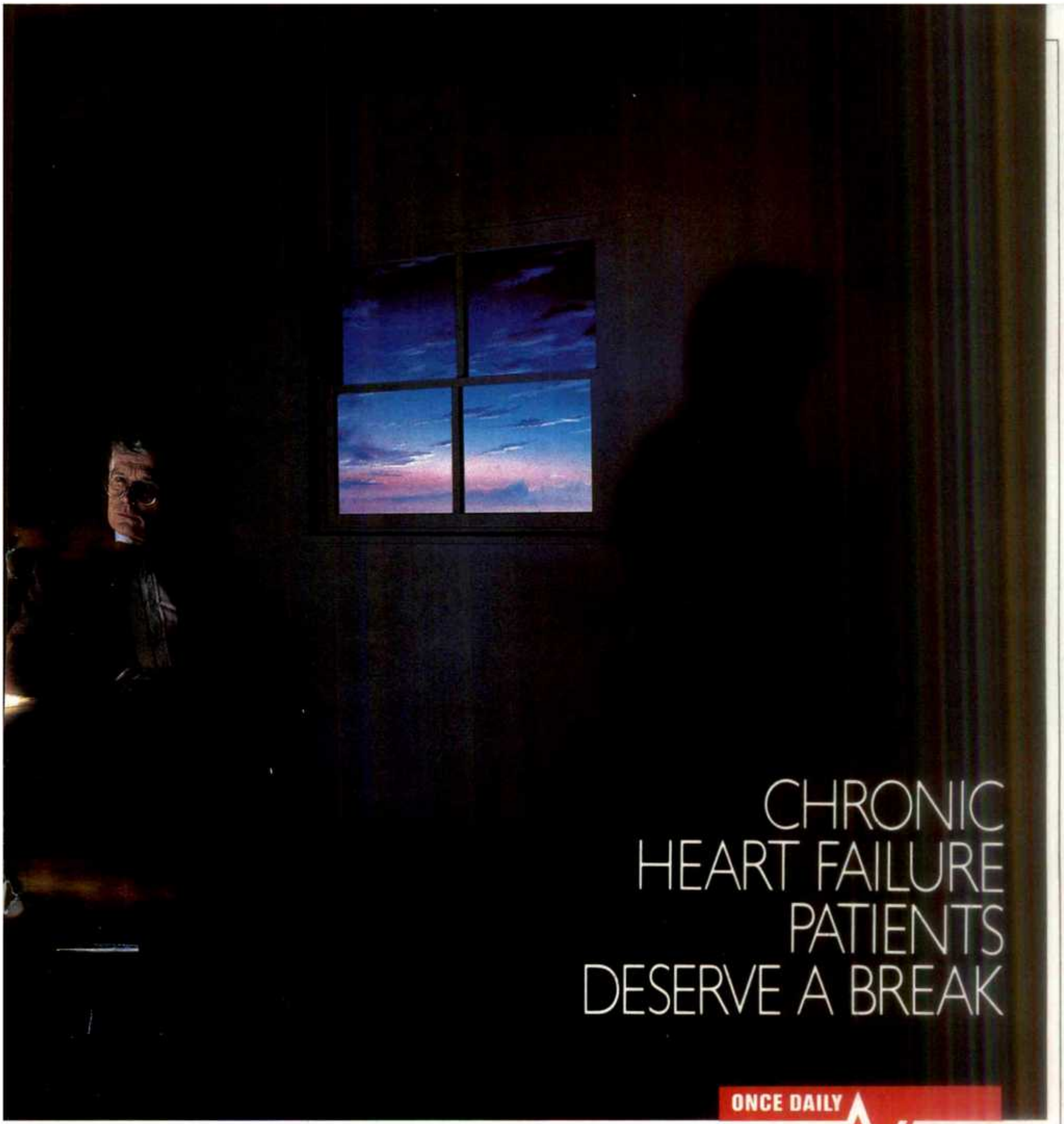

A sustained break from their symptoms

'Innovace' may provide moderate to severe heart failure patients, even those clinically stable on diuretic therapy, with significant symptomatic improvement.

This symptomatic improvement, in parameters such as decreased breathlessness and increased exercise capacity, is sustained. However, it is important to exercise care in treating heart failure patients, particularly those who are severely ill and on high doses of diuretics.

Blood pressure and renal function should be monitored closely, both before and during treatment, because hypotension and renal impairment can occur. Reducing the dose of diuretics and starting therapy in hospital under close supervision with the recommended low dose of 2.5 mg of 'Innovace' helps minimise the incidence of early hypotension and facilitates initiation of therapy. Using 'Innovace' to break the *'vicious circle'* can go a long way to offer chronic heart failure patients benefits they may have not thought possible.

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USES

All grades of essential hypertension and renovascular hypertension where standard therapy is ineffective or inappropriate because of adverse effects.

In congestive heart failure, as adjunctive therapy with digitalis and diuretics, treatment should always be initiated in hospital.

DOSAGE

Essential and renovascular hypertension: Therapy should be initiated with 5 mg in patients under 65 years of age; 2.5 mg if older or in presence of renal impairment. The usual maintenance dose is 10–20 mg once daily; maximum 40 mg once daily. When adding to a diuretic, the starting dose of 'Innovace' is 2.5 mg with the diuretic discontinued for 2–3 days prior to 'Innovace', if possible.

Reduce beta-blocker dose gradually after starting 'Innovace'. Dose titrate to BP requirements. Dosage of other antihypertensives may need adjusting.

Congestive heart failure: Can be used as adjunctive therapy with diuretics and, where appropriate, digitalis. Initial daily dose 2.5 mg under close supervision in hospital. If possible, diuretic dose should be reduced beforehand. Monitor blood pressure closely for hypotension.

Increase dose gradually to usual maintenance dose of 10–20 mg daily.

MODE OF ACTION

Following oral administration, 'Innovace' is rapidly absorbed and hydrolysed to enalaprilat, a highly specific, long-acting, non-sulphydryl angiotensin-converting enzyme inhibitor.

CONTRA-INDICATIONS

Pregnancy: assessment for possible pregnancy required if menstrual period is missed. Hypersensitivity.

PRECAUTIONS

Assess renal function prior to therapy with 'Innovace' and during treatment where appropriate. Should not be given with aortic stenosis or outflow tract obstruction.

Symptomatic hypotension is more likely following volume depletion caused by diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting or in patients with congestive heart failure with or without renal insufficiency. Severe hypotension reported mainly in patients with severe heart failure.

Impaired renal function: Caution should be used in patients with renal impairment. Renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Renal failure has been reported, mainly in patients with severe congestive heart failure or underlying renal disease, and is usually reversible. Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying artery stenosis. 'Innovace' is dialysable.

Renovascular hypertension: 'Innovace' can be used when surgery is not indicated or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases in blood urea and creatinine, reversible upon discontinuation of therapy, have been seen.

Because it is not known whether 'Innovace' is excreted in human milk, caution required if given to nursing mothers. Has not been studied in children.

Surgery/anaesthesia: 'Innovace' may lead to hypotension requiring volume expansion.

Drug interactions: Increased antihypertensive effect when combined with methyldopa, beta-blockers, calcium antagonists, or diuretics. Adrenergic-blocking drugs should be added with caution. Concomitant propranolol may reduce bioavailability. Lithium levels may be increased.

Plasma potassium usually remains within normal limits. 'Innovace' may elevate plasma potassium levels in patients with renal failure. Potassium supplements or potassium-sparing diuretics are not usually recommended, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. If deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

SIDE EFFECTS

Severe hypotension and renal failure.

Angioneurotic oedema has occurred rarely. Discontinue 'Innovace'; condition usually resolves without treatment, but give subcutaneous adrenaline (0.5 ml 1:1,000) if airways obstruction likely.

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Serum β-enolase in acute myocardial infarction

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SUMMARY The enzyme β-enolase (αβ and ββ forms) is present in skeletal and heart muscle and catalyses the glycolysis of 2-phosphoglycerate to phosphoenolpyruvate. The enzyme was measured in serum samples from patients with acute myocardial infarction, angina pectoris, congestive heart failure, and idiopathic cardiomyopathy. Serum concentrations of β-enolase were significantly increased in acute myocardial infarction but not in the other cardiovascular diseases. Activity peaked approximately 12 to 14 hours after an acute attack of chest pain, and then gradually decreased as the patient recovered. The rise and fall in β-enolase concentration were faster and steeper than those of creatine kinase activity, particularly in patients in whom activities of both these enzymes were less high. The assay of β-enolase, which is highly specific and sensitive, has considerable advantages for the early diagnosis of myocardial infarction and the diagnosis of a second episode of myocardial infarction because β-enolase concentration increases very early and rapidly and clears quickly.

These data imply that serum β-enolase may be a more effective marker for early myocardial infarction, particularly in milder cases, than measurement of creatine kinase activity.

Mammalian enolase (2-phospho-D-glycerate hydrolase, EC 4.2.1.11) occurs as dimers composed of three immunologically distinct subunits—α, β, and γ.[1 2] γ-enolase (αγ and γγ forms) is found in neuronal tissues and neuroendocrine cells and β-enolase (αβ and ββ forms) is found mainly in heart and skeletal muscle.[3 4] The characteristic distribution of these enolases suggests that they may be useful as disease markers.[3 4]

Using a sensitive enzyme immunoassay method Kato *et al* have recently confirmed that β-enolase in serum is a useful marker for human muscle diseases.[5] We have measured immunoreactive β-enolase in serum samples from patients with various cardiovascular diseases to determine whether this enzyme could be used as a marker for acute myocardial infarction.

Patients and methods

We studied 26 consecutive patients (aged 38–84, 21 men and 5 women) with a first acute attack of myocardial infarction and without neuromuscular diseases. They were admitted to the coronary care unit of our hospital. We also studied 10 patients (all men, aged 36–61) with angina pectoris, eight with congestive heart failure not caused by acute myocardial infarction, and three patients with idiopathic cardiomyopathy. Cardiac disease was diagnosed by the attending cardiologist according to standard criteria, which included clinical history, electrocardiographic and echocardiographic changes, and biochemical assessment. We excluded patients with cardiogenic shock and those on cardiotonic medication, except for dopamine, which did not affect this enzyme. We also studied 20 normal subjects (15 men and 5 women, aged 20–70) and 10 patients with renal failure or hepatic disease. Blood samples were collected every two hours for 34 hours after admission from the cubital vein via an indwelling tube contain-

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ing anticoagulant. Within 30 minutes of collection serum was separated from the blood samples by centrifugation at 3000 rpm for 10 minutes. Plasma was obtained from citrated blood by centrifugation.

We used the β-enolase immunoassay described by Kato *et al.*[4] The assay system uses polystyrene spheres coated with immobilised purified antibodies to β subunit and β subunit antibodies labelled with β D-galactosidase from *Escherichia coli*. The β-enolase assay is specific and there is no cross-reaction with other forms of enolase.[5] Intramuscular injections and cardioversion did not markedly alter concentrations of serum β-enolase.

Serum creatine kinase (EC 2.7.3.2) activity was assayed spectrophotometrically with Testomar-C CK mono from Calbiochem-Behring, or a Centrifi-Chem CK reagent set from Baker Instruments Co, by coupling the reaction with hexokinase and glucose-6-phosphate dehydrogenase.[6] The normal value of total creatine kinase activity is <35 mU/ml.

Technetium-99m pyrophosphate scintigraphy of the myocardium was carried out according to the method of Bonte *et al*[7 8] in order to assess the size of the infarct. There was a good correlation between infarct size and creatine kinase activity; $y = 12{\cdot}2x - 12{\cdot}8$, $r = 0{\cdot}81$, $p < 0{\cdot}001$).

Patients with acute myocardial infarction were divided into two groups. Those in whom the concentration of β-enolase was normal on admission and peak creatine kinase activity (≤300 mU/ml) and peak β-enolase concentration (≤110 ng/ml) tended to be low were identified as mild cases. Those with a higher than normal concentration of β-enolase on admission, higher peak of creatine kinase activity (>300 mU/ml), and peak β-enolase (>110 ng/ml) concentration were defined as severe cases. There were 13 patients in each group.

Results

The mean (SD) serum concentration of β-enolase in the 20 normal subjects was 5·6 (3·1) ng/ml (range 1·6–16·7 ng/ml). Concentrations of β-enolase were normal in haemolysed serum samples. In the 26 patients with acute myocardial infarction the serum concentration of β-enolase correlated well with serum creatine kinase activity ($y = 0{\cdot}41x + 34{\cdot}67$, $r = 0{\cdot}813$).

The peak concentration of β-enolase in serial serum samples from patients with acute myocardial infarction was significantly raised (4–22 times higher than the normal value) (figs 1 and 2). β-enolase concentration peaked 12–14 hours after an acute attack of chest pain lasting more than an hour and then gradually fell during recovery. Changes in serum β-enolase concentration resembled changes in serum creatine kinase activity in acute myocardial infarction (figs 1 and 2). In 13 mild cases the increase in β-enolase concentration occurred before the increase in creatine kinase activity and the rise and fall in β-enolase concentration were steeper than those of creatine kinase activity (fig 1a and b). Comparison of the t^{α} values of the gamma variate function for the changes in β-enolase concentration and creatine kinase activity confirmed these data. In 13 severe cases the difference in the increase in β-enolase concentration and creatine kinase activity showed a

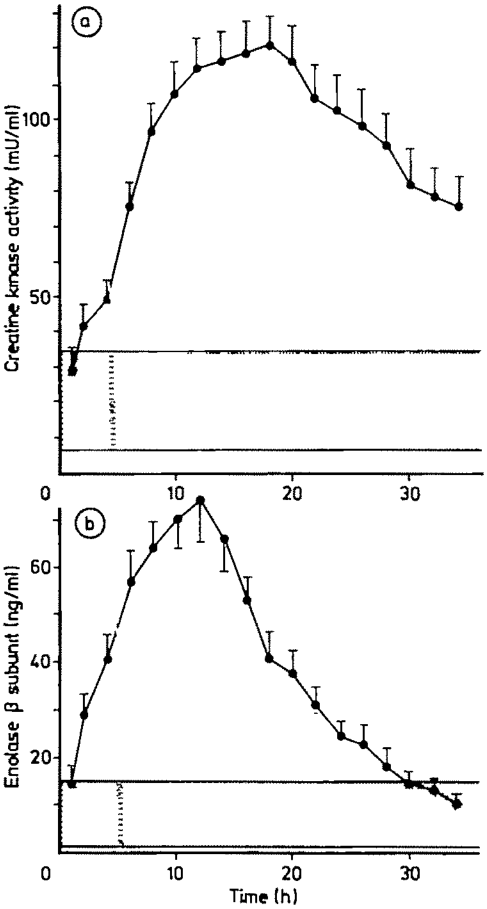

Fig 1 *Mean (SE) serum β-enolase concentration and creatine kinase activity in 13 patients with mild acute myocardial infarction. Increases in creatine kinase activities or β-enolase concentration were significantly higher than normal from 6 to 32 hours and from 4 to 26 hours respectively after the onset of acute myocardial infarction. (Student's t test for paired values.) Normal values are shown by the shaded area.*

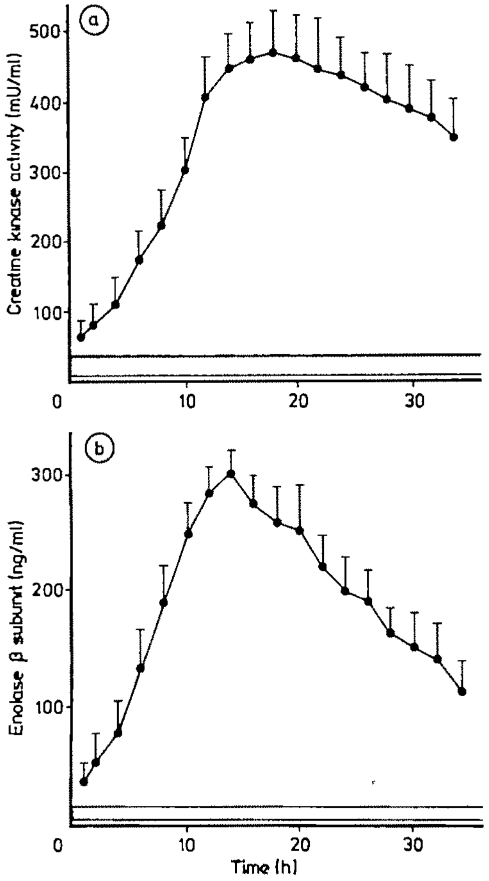

Fig 2 *Mean (SE) serum β-enolase concentrations and creatine kinase activity in 13 patients with severe acute myocardial infarction. Increases in creatine kinase activity and β-enolase concentrations were significantly higher than normal from 4 to 34 hours and from 2 to 34 hours respectively after the onset of acute myocardial infarction. Normal values are shown by the shaded area.*

similar pattern to that in the mild cases. In the patients with normal enzyme activity on admission serum β-enolase concentration was higher than normal for a shorter time (3·1 (1·5)h) than creatine kinase activity (6·1 (2·0)h) (fig 3) and the mean interval between onset of the symptoms and peak β-enolase was significantly shorter (12·3 (0·7)h in mild cases and 14·6 (1·0)h in severe cases) than the interval to peak creatine kinase activity (16·6 (0·7)h in mild cases and 18·6 (1·3)h in severe cases). Serum concentrations of β-enolase did not rise in patients with angina pectoris or other heart diseases, in those with acute hepatitis or renal failure, or in healthy subjects after exercising on a treadmill (table).

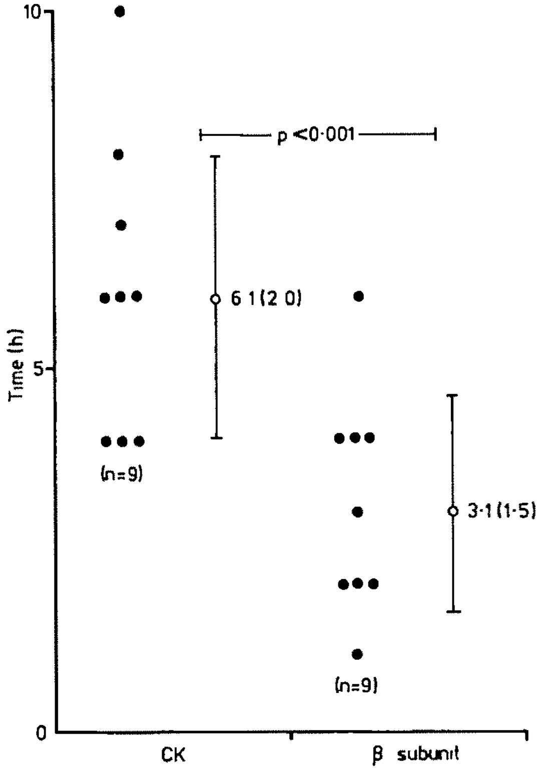

Fig 3 *Comparison (by Student's t test for non-paired values) of periods during which serum β-enolase concentration or creatine kinase activity were higher than normal in patients with acute myocardial infarction. Means (SD) are shown.*

Although the mean value in patients with acute hepatitis was twice that in normal subjects, most values came within the limits of normal variation (mean ± 2SD). We found a significant (p < 0·05) cor-

Table *Mean (SE) β-enolase concentration in normal subjects before and after treadmill exercise and in patients with cardiovascular, hepatic, or renal disease*

	β-enolase concentration (ng/ml)*
Normal subjects (20)	5·6 (1·4)
Treadmill exercise test (7).	
Before	4·2 (1·0)
After	4·6 (0·9)
Angina pectoris (10)	5·2 (1·0)
Congestive heart failure (8)	4·0 (0·8)
Idiopathic cardiomyopathy (3)	2·1 (0·5)
Acute hepatitis and liver cirrhosis (10)	10·8 (2·6)
Renal failure (10)	3·3 (0·5)

*ββ enolase equivalent

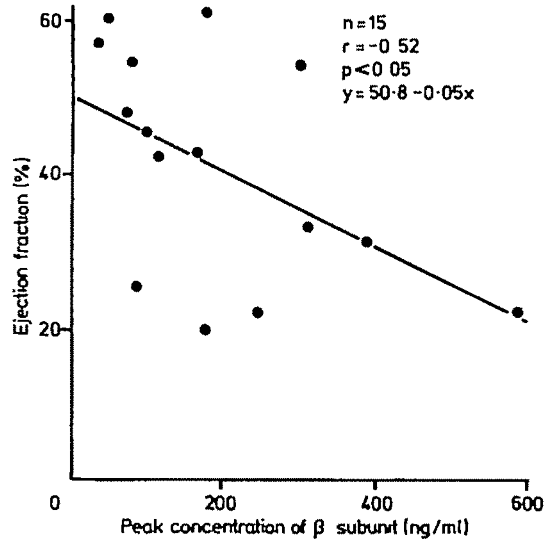

Fig 4 *Correlation between peak serum concentrations of β-enolase and ejection fraction in patients with acute myocardial infarction (mild and severe cases).*

relation between the peak concentration of β-enolase and ejection fraction (fig 4) and infarct size measured by scintigraphy both in mild and severe cases.

Discussion

Many investigators have reported an increase in the activity of several enzymes in the serum of patients with acute myocardial infarction and have confirmed a relation between peak activity of the serum enzyme (particularly creatine kinase) and the size of the myocardial infarct.[9–13] The activity of glycolytic enzymes, such as pyruvate kinase[14–16] and enolase[16,17] was also reported to be increased in acute myocardial infarction. But serum β-enolase had not been evaluated as a marker in acute myocardial infarction. We used a highly sensitive assay for β-enolase. We demonstrated that the concentration of serum β-enolase rose in an early phase of acute myocardial infarction. The increase correlated well with changes in creatine kinase activity and the increase in β-enolase was specific for acute myocardial infarction; it did not occur in patients with other kinds of heart disease who did not have concurrent neuromuscular disorders in which serum concentrations of β-enolase are raised.[18]

Serum concentrations of β-enolase were normal in patients with acute hepatitis and renal failure, which suggests that the increase that we found in patients with myocardial infarction was not caused by a decrease in the degradation rate of this enzyme. We believe that release from necrotic heart muscle rather than from blood cells accounts for the increase in β-enolase because β-enolase is not found in blood cells.

The peak concentration of β-enolase paralleled that of creatine kinase MB[19,20] and myoglobin.[20,21] The β-enolase assay system may be more simple and sensitive than assays for creatine kinase and myoglobin. A very early and rapid increase in concentration after the onset of infarction and a quick clearance may make β-enolase a better marker than creatine kinase for the early diagnosis of infarction and the diagnosis of a second episode of necrosis occurring more than a day after the first episode. In cases of acute myocardial infarction in which creatine kinase activity is not very high it may be difficult to detect myocardial infarction, and in such patients the assessment of serial changes in serum β-enolase concentration may be more useful for the early detection of acute myocardial infarction.

The time required to assay β-enolase concentrations can be reduced to less than an hour if the reaction temperature is raised and the size of the polystyrene balls is increased.[4] This enzyme immunoassay is cheaper than a radioimmunoassay and does not require radioactive reagents.

Serum β-enolase concentration has been used successfully to estimate the size of myocardial infarcts produced in dogs by experimentally induced myocardial infarction (unpublished observations).

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References

1 Rider CC, Taylor CB. Enolase isoenzymes in rat tissues. Electrophoretic, chromatographic and kinetic properties. *Biochim Biophys Acta* 1974;365:285–300.
2 Fletcher L, Rider CC, Taylor CB. Enolase isoenzymes. III. Chromatographic and immunological characteristics of rat brain enolases. *Biochim Biophys Acta* 1976;452:245–52.
3 Taylor CB, Royds JA, Parsons MA, Timperley WR. Diagnostic aspects of enolase isozymes. *Isozymes Curr Top Biol Med Res* 1983;11:95–119.
4 Kato K, Ishiguro Y, Ariyoshi Y. Enolase isozymes as disease markers: distribution of three enolase subunits (α, β, and γ) in various human tissues. *Disease Markers* 1983;1:213–20.
5 Kato K, Okagawa Y, Suzuki F, Shimizu A, Mokuno K, Takahashi Y. Immunoassay of human muscle enolase subunit in serum: a novel marker antigen for muscle diseases. *Clin Chim Acta* 1983;131:75–85
6 Bondar RJL, Mead DC. Evaluation of glucose-6-

phosphate dehydrogenase from *Leuconostoc mesenteroides* in the hexokinase method for determining glucose in serum. *Clin Chem* 1974;**20**:586–90.

7 Bonte FJ, Parkey RW, Graham KD, Moore J, Stokely EM. A new method for radionuclide imaging of myocardial infarcts. *Radiology* 1974;**110**:473–74.

8 Kondo T, Kiriyama T, Kato Y, *et al*. Evaluation of an infarct area using technetium-99m pyrophosphate myocardial scintigraphy [in Japanese]. *J Cardiogr* 1982;12:699–708.

9 LaDue JS, Wroblewski F, Karmen A. A serum glutamic oxaloacetic transaminase activity in human acute transmural myocardial infarction. *Science* 1954,120.497–9.

10 Hess B. DPN-dependent enzymes in serum. *Ann NY Acad Sci* 1958;75:292–303.

11 Sobel BE, Brenahan GF, Shell WE, Yoder RD. Estimation of infarct size in man and its relation to prognosis *Circulation* 1972;**46**:640–8.

12 Norris RM, Whitlock RML, Barratt-Boyes C, Small CW. Clinical measurement of a method for the estimation of total creatine phosphokinase release after myocardial infarction. *Circulation* 1975;51:614–20.

13 Nagasaka A, Nishizima K, Hidaka H, *et al*. Serum cyclic 3′, 5′-nucleotide phosphodiesterase activity in myocardial infarction. *Acta Cardiol (Brux)* 1985;**11**:613–20.

14 Harano Y, Adair R, Vignos PJ Jr, Miller M, Kowal J. Pyruvate kinase isoenzymes in progressive muscular dystrophy and in acute myocardial infarction. *Metabolism* 1973;**22**.493–501.

15 Shaft FR, Ban RW, Imfeld H. Serum pyruvate kinase in acute myocardial infarction. *Am J Cardiol* 1970;**26**:143–50.

16 Herraez-Dominguez M, Goldberg DM, Anderson AJ, Fleming JS, Rider CC, Taylor CB. Serum enolase and pyruvate kinase activities in the diagnosis of myocardial infarction. *Enzyme* 1976;**21**:211–24.

17 Herraez-Dominguez M, Goldberg DM, Greaves M, Fleming JS, Rider CC, Taylor CB. Immunological determination of muscle-type enolase in the serum as a diagnostic test for myocardial infarction. *Clin Chim Acta* 1975;**64**:307–15.

18 Mokuno K, Riku S, Matsuoka Y, Sobue I, Kato K. Serum muscle-specific enolase in progressive muscular dystrophy and other neuromuscular diseases. *J Neurol Sci* 1984;**63**:345–52.

19 Wagner GS, Roe CR, Limbird LE, Rosati RA, Wallance AG. The importance of identification of the myocardial-specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction. *Circulation* 1973;47:263–9.

20 Catheline M, Bouget J, Aubree A, Daubert C, Gouffault J, Legall JY. Etude de la myoglobinemie et de son evolution au cours de l'infarctus du myocarde. *Clin Chim Acta* 1980;**105**:311–5.

21 Grachev MA, Matveev LE, Pressman EK, Roschke VV. A rapid method for myoglobin radioimmunoanalysis as a diagnostic tool in myocardial infarction. *Clin Chim Acta* 1982;**124**:235–8.

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A comparison of symptoms and intra-arterial ambulatory blood pressure during long term dual chamber atrioventricular synchronous (DDD) and ventricular demand (VVI) pacing

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SUMMARY Fifteen patients with dual chamber pacemakers implanted for atrioventricular block (11) or sinoatrial disease (4) completed a single blind within-patient comparison of symptoms and 24 hour intra-arterial blood pressure during long term atrioventricular synchronous (DDD) pacing and long term ventricular demand (VVI) pacing. The patients reported significantly less breathlessness, fatigue, and dizziness and a significantly greater sense of general well-being during DDD pacing than during VVI pacing. Twelve of the fifteen patients expressed a strong preference for DDD pacing. Systolic blood pressure tended to be lower and was significantly more variable during VVI pacing than during DDD pacing (mean (SD) daytime systolic blood pressure 132·4 (17·1) and 140·4 (13·1) mm Hg respectively). Accordingly, episodes of hypotension were more common during VVI pacing, which may partly explain why the patients reported more symptoms during this mode of pacing.

Dual chamber or atrioventricular synchronous (DDD) pacing has several theoretical advantages over ventricular demand (VVI) pacing.[1] These include the ability of DDD pacing to maintain the normal activation sequence of atrial and ventricular systole and to provide a degree of rate responsiveness.

Several groups have shown that in patients with atrioventricular conduction block, long term atrioventricular synchronous pacing produces better haemodynamic function,[2] a greater effort tolerance,[2–4] and fewer symptoms[3 4] than long term ventricular demand pacing. There is also evidence that patients who require pacing for sinoatrial disease experience fewer symptoms during atrioventricular sequential pacing than during ventricular demand pacing.[5] Because most patients receiving pacemakers are elderly, the maximum effort tolerance achieved during a treadmill test is probably of little relevance to their daily life. However, any improvement in symptoms such as dizziness, shortness of breath, or in general well-being is clearly worth while.

In some patients ventricular demand (VVI) pacing can induce episodes of pronounced symptomatic hypotension,[6 7] a condition often known as the pacemaker syndrome. Atrioventricular synchronous (DDD) pacing may help to prevent such attacks, at least in patients with the carotid sinus syndrome.[8] Some of the symptoms reported during ventricular demand pacing, particularly minor dizzy spells, may be due to less florid forms of this phenomenon. We have, therefore, compared symptoms and intra-arterial 24 hour ambulatory blood pressure in a group of unselected patients during long term dual chamber (DDD) and long term ventricular demand (VVI) pacing. Some of these data have been presented in preliminary form at the British Cardiac Society.[9]

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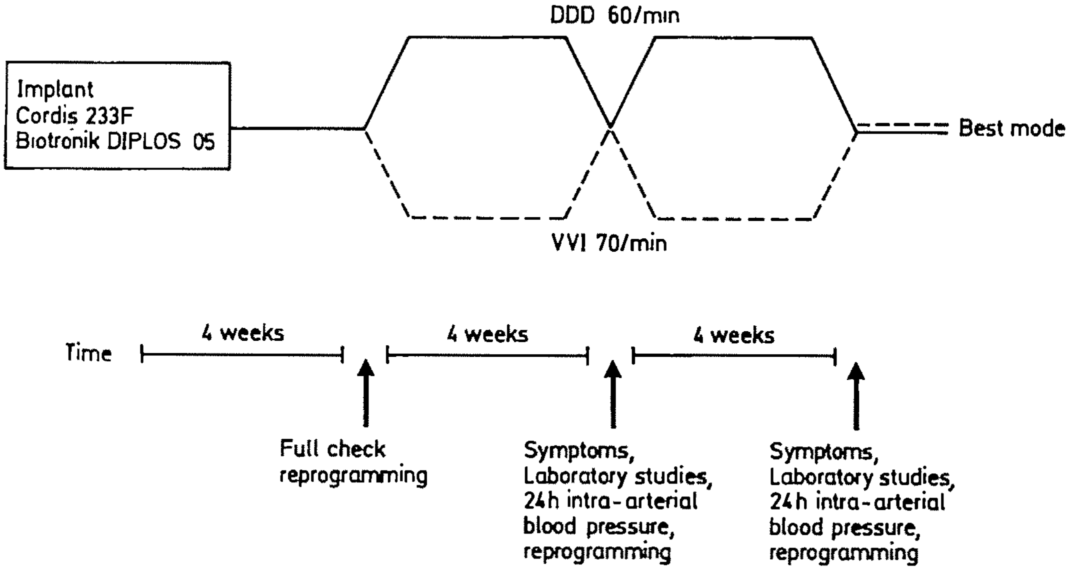

Fig 1 *Design of the study.*

Patients and methods

PATIENT SELECTION

Dual chamber pacemakers (Cordis 233F or Biotronic Diplos 05) were implanted in a group of 18 patients chosen at random from those receiving pacemakers at the John Radcliffe Hospital during the period of the study. The indications for pacing were: complete heart block and syncope (6), complete heart block with presyncope or shortness of breath (3), asymptomatic complete heart block (1), left bundle branch block and syncope (1), sinoatrial disease with syncope (3), sinoatrial disease with presyncope (1). The only exclusion criteria were the presence of atrial fibrillation or angina on effort. Patients were invited to take part in the study when they came to the hospital for routine checks one month after implantation of the pacemaker. Informed written consent was obtained in every case and the study was approved by the Central Oxford Regional Ethics Committee.

PROTOCOL

Figure 1 shows the design of the study. After recruitment, patients were randomly allocated, single blind, to either VVI pacing at a rate of 70 or 72 per minute or DDD pacing with a back up rate of 60 per minute (the atrioventricular delay and atrial refractory period were selected by the cardiologist in charge of the case). After an equilibration period of at least four weeks each patient underwent a symptom assessment and a 24 hour ambulatory recording of the electrocardiogram and intra-arterial pressure. The pacemaker was then programmed to the opposite mode and the observations were repeated after a further equilibration period of at least four weeks. Several laboratory measurements were made immediately before each 24 hour blood pressure recording and these will be the subject of a separate report. At the end of the study the pacemaker was reprogrammed to the DDD mode unless the patient had expressed a strong preference for VVI pacing.

DATA COLLECTION

Symptom assessment

Shortness of breath, dizziness, fatigue, and general well-being were assessed at each visit on a 10 cm visual analogue scale. At the end of the study patients were asked to express a preference for one of the two forms of pacing.

24 hour ambulatory blood pressure and electrocardiogram recording

The Seldinger technique was used to place a Teflon cannula (internal diameter 1 mm, Plastimed) in the brachial artery of the non-dominant arm. This was connected to a portable perfusion pump, transducer, and miniature analogue tape recorder (Oxford Medilog).[10] The surface electrocardiogram and pacemaker spike were recorded on additional channels of the tape recorder.

Patients were asked to keep a diary of the day's events and were encouraged to remain as active as possible during the period of the recording. All but four patients returned to their homes for the duration of the recording; those who stayed in hospital remained ambulant during the day. In every case one of the investigators checked the apparatus carefully immediately before the patient retired to bed. Unfortunately, in three cases the cannula became partly or completely blocked during the night; the nocturnal records for these patients were excluded from the final analysis.

DATA ANALYSIS

Beat to beat analyses of the 24 hour blood pressure and electrocardiogram records were made with an Eclipse S200 computer programmed to analyse the systolic blood pressure, diastolic blood pressure, arithmetic mean blood pressure, and RR interval. Data collected while the patients were asleep were analysed separately from data collected while they were awake.

STATISTICAL METHODS

We used Student's paired *t* test to compare differences in blood pressure and the Wilcoxon signed rank test for paired data to compare differences in all other variables.

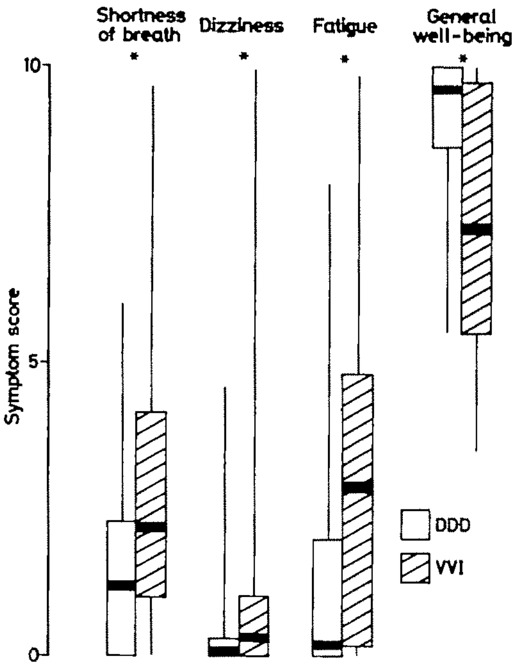

Fig 2 *Symptom scores during DDD and VVI pacing. Data are presented as the median (bar), interquartile range (box), and full range of values. *$p < 0.05$ Wilcoxon signed rank test; n = 15.*

Results

PATIENT DETAILS

Eighteen patients entered the study but we withdrew three patients after they completed the first limb of the study. One of these three patients was withdrawn from the study because he was found to have a disseminated malignant tumour. Angina developed in the other two; in one this was associated with a change from DDD to VVI pacing and in the other it was associated with a change from VVI to DDD pacing.

Fifteen patients (13 men, 2 women) completed the study. Of these, seven were allocated to VVI pacing followed by DDD pacing and eight were allocated to DDD pacing followed by VVI pacing. The mean age of these patients was 69 years (range 54–81 years).

Two patients with sinoatrial disease and one patient with complete heart block had demonstrable ventriculoatrial conduction at the time of the pacemaker implant. A fourth patient, who was paced for sinoatrial disease, was shown to have intermittent ventriculoatrial conduction during the course of the

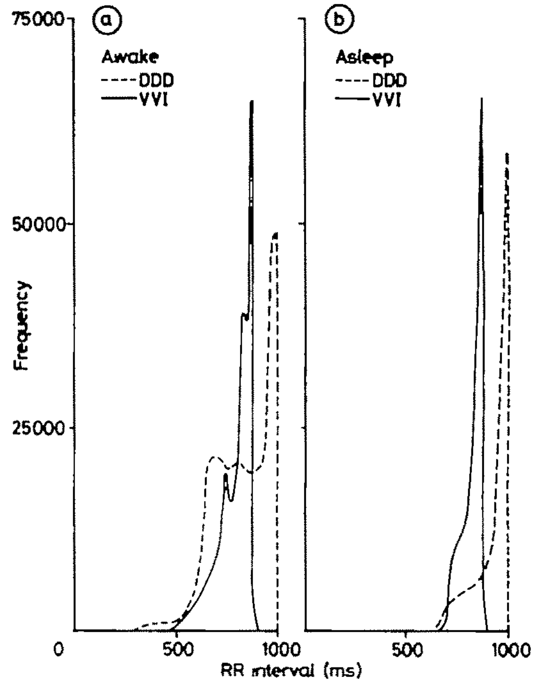

Fig 3 *Distribution of the RR interval, defined to the nearest 8 ms, during DDD and VVI pacing during wakefulness (n = 15) and sleep (n = 12). The data are presented as a frequency histogram that includes every recorded heart beat in every patient.*

Table *Mean (SD) blood pressure while patients were awake or asleep*

	VVI pacing	*DDD pacing*
Awake (n = 15).		
Systolic BP	132·4 (17·1)	140·4* (13·1)
Mean BP	94·2 (14·4)	97·9 (9·9)
Diastolic BP	74·4 (13·1)	74·7 (10·3)
Asleep (n = 12).		
Systolic BP	118·2 (17·7)	119·5 (14·9)
Mean BP	85·6 (10·8)	85·0 (11·6)
Diastolic BP	68·0 (7·7)	64·2 (11·6)

*p < 0·02, Student's paired *t* test. BP, blood pressure

study. In the other eleven patients ventriculoatrial conduction was not seen.

SYMPTOMS

The patients, as a group, reported significantly less shortness of breath, dizziness, and fatigue during DDD pacing (fig 2). DDD pacing was also associated with a significantly greater sense of general well-being (fig 2). At the end of the study twelve patients expressed a strong preference for DDD pacing, two patients expressed no preference, and one patient expressed a strong preference for VVI pacing.

HEART RATE AND RHYTHM

Figure 3 shows the distribution of the RR interval (measured to the nearest 8 ms) during VVI and DDD pacing while the patients were asleep and awake. The data are presented as a cumulative frequency histogram for all fifteen patients. During VVI pacing the pacing rate was either 70 or 72 per min whereas during DDD pacing the back up rate was 60 per min. The median values for the daytime RR intervals during DDD (805 ms) and VVI (828 ms) pacing were not significantly different. There was a much greater range of RR interval during DDD pacing. At night the median RR interval was significantly longer during DDD (946 ms) pacing than during VVI (844 ms) pacing (p < 0·01, Wilcoxon signed rank test).

Analysis of individual records showed that during VVI pacing all but one patient experienced nearly continuous ventricular pacing. The remaining patient was in sinus rhythm for most of the time. Three other patients had episodes of sinus rhythm during the 24 hour period; a further three patients experienced quite frequent (> 1 per min) ventricular ectopic complexes and one patient had very frequent (> 3 per min) ventricular ectopic complexes. During DDD pacing two patients experienced short runs of pacemaker mediated tachycardia. The maximum tracking rate of the pacemaker, which ranged from 92 to 150 beats/min (650–400 ms RR interval) (median value 108 beats/min (550 ms RR interval)), was achieved at least once during the 24 hours in six of the 15 patients.

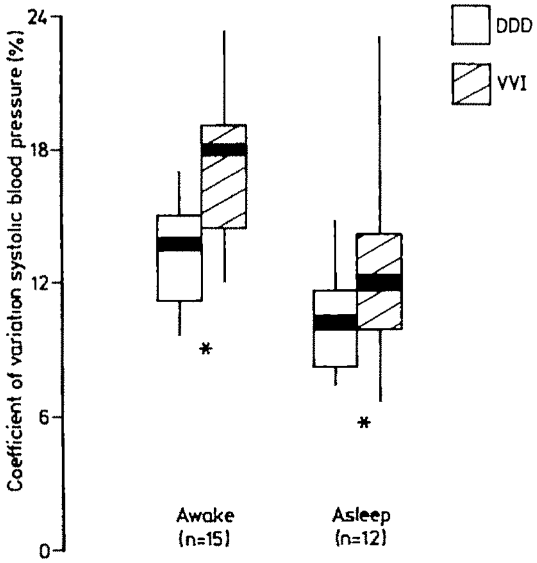

Fig 4 *Coefficients of variation for systolic blood pressure during DDD and VVI pacing during wakefulness (n = 15) and sleep (n = 12). The data are presented as the median (bar), interquartile range (box), and full range of values. *p < 0·01 Wilcoxon signed rank test.*

BLOOD PRESSURE

The table gives the mean (SD) systolic, diastolic,

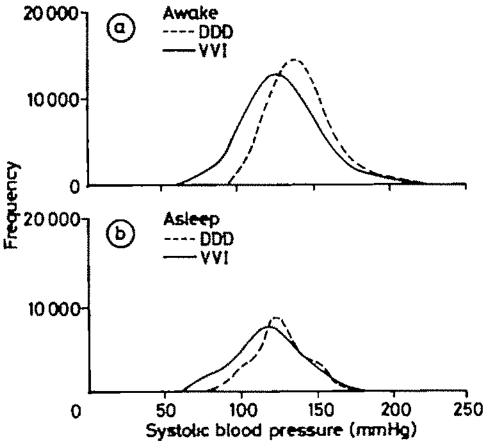

Fig 5 *Distribution of the systolic blood pressure, measured to the nearest mm Hg, during DDD and VVI pacing during wakefulness (n = 15) and sleep (n = 12). The data are presented as a frequency histogram that includes every recorded heart beat in every patient.*

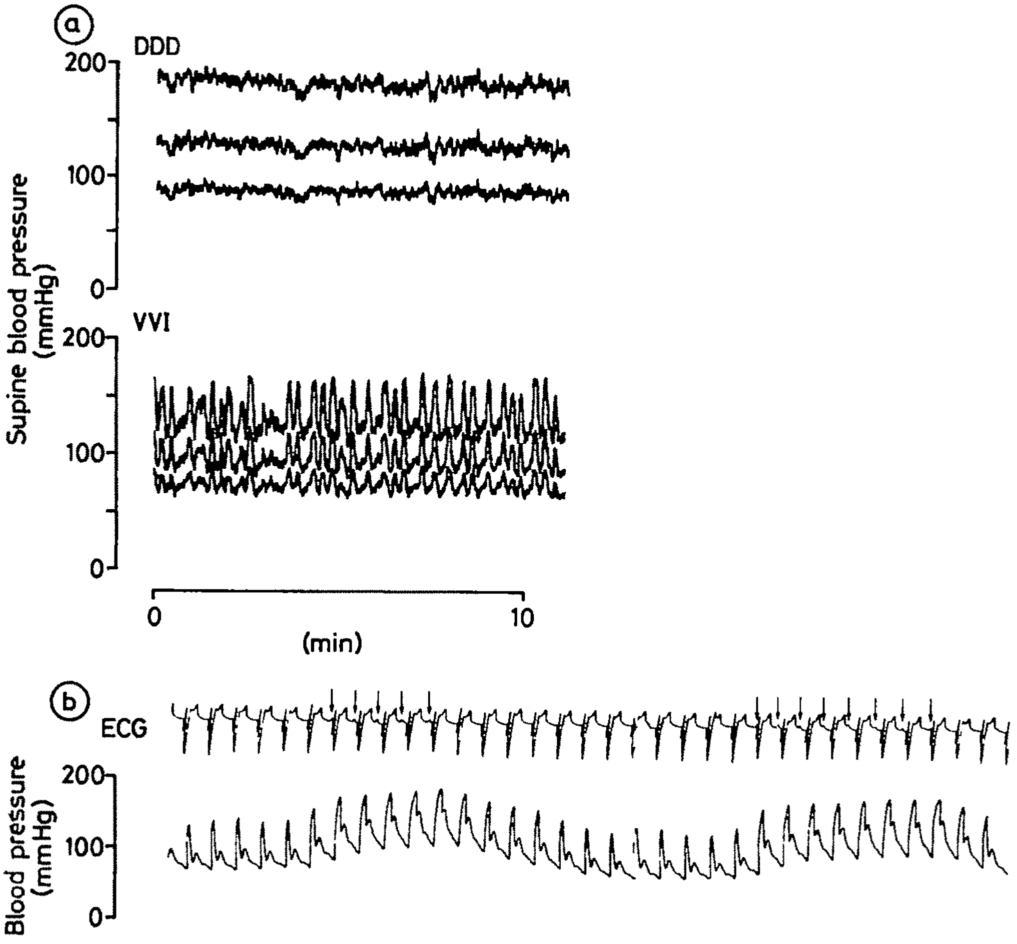

Fig 6 (*a*) *Computer generated trend recording of systolic, arithmetic mean, and diastolic intra-arterial blood pressure during DDD and VVI pacing in the same patient lying supine at the same time of day. (b) Higher speed recording of the intra-arterial blood pressure during VVI pacing shown in (a) together with the electrocardiogram in which the P waves are identified by arrows.*

and arithmetic mean blood pressures during DDD and VVI pacing. Systolic blood pressure tended to be lower during VVI pacing and this difference was significant ($p < 0.02$, Student's paired *t* test) for the period when the patients were awake.

BLOOD PRESSURE VARIABILITY

The coefficients of variation for systolic blood pressure during wakefulness and sleep were considerably greater during VVI pacing than during DDD pacing (fig 4). In every patient the difference favoured DDD pacing. The coefficients of variation for mean and diastolic blood pressures were also significantly greater during VVI pacing than during DDD pacing (data not shown).

Figure 5 shows the distribution of the systolic blood pressures (to the nearest mm Hg) during the two modes of pacing. The greater variability in systolic blood pressure during VVI pacing is evident. The data are presented as a frequency histogram of the systolic blood pressure for every heart beat in every patient. These curves clearly demonstrate that the mean systolic blood pressure was slightly lower during VVI pacing than during DDD pacing and that the range of systolic blood pressure was much greater during VVI pacing than during DDD pacing. Accordingly there were more episodes of systolic hypotension during VVI pacing. While very few heart beats produced a systolic blood pressure of <100 mm Hg during DDD pacing, approximately

80 000 heart beats produced a systolic blood pressure of < 100 mm Hg during VVI pacing.

Figure 6 shows short recordings of the blood pressure during VVI and DDD pacing in the same patient under the same conditions. The greater blood pressure variability during VVI pacing is obvious and in this case can be clearly related to the presence of atrioventricular dissociation.

Discussion

This study has confirmed that most patients experience fewer symptoms during long term atrioventricular pacing than during long term ventricular demand pacing.[3-5] This may be the result of several factors such as the absence of cannon waves, better haemodynamic function, and better control of blood pressure. The patients who took part in this study are representative of patients treated by permanent pacing at this centre. It therefore appears that DDD pacing may offer additional benefit to a wide group of patients.

Our findings demonstrate, beyond doubt, that long term DDD pacing gives better control of blood pressure with fewer episodes of hypotension than long term VVI pacing. Indeed, DDD pacing in our patients produced average values for intra-arterial ambulatory blood pressure and blood pressure variability that are very similar to those reported in a group of healthy elderly normotensive subjects.[11] In contrast, VVI pacing was associated with a significantly lower and significantly more variable blood pressure and, therefore, with more frequent episodes of hypotension. It seems likely that some of the symptoms reported during the period of VVI pacing were caused by these episodes of hypotension. Certainly, at times the blood pressure fell below the likely lower limit of cerebral autoregulation.[12] Unfortunately we do not know whether or not our patients' symptoms coincided with episodes of hypotension. This is partly because we asked our patients to report symptoms that had occurred in the month before the 24 hour blood pressure recording and partly because in most cases the symptoms experienced during VVI pacing were ill-defined and could not be timed accurately.

The pronounced increase in blood pressure variability seen during VVI pacing, compared with that seen during DDD pacing or in elderly normotensive subjects,[11] is almost certainly caused by atrioventricular dissociation. Figure 6b shows how changes in the relative timing of atrial and ventricular systole can produce profound changes in blood pressure. The fact that VVI pacing was associated with greater blood pressure variability than DDD pacing, even when patients were asleep and paced virtually continuously (fig 3), provides strong evidence that this difference is a function of atrioventricular dissociation rather than rate responsiveness. There may, therefore, be a similar increase in blood pressure variability in patients treated with rate-responsive VVI pacemakers.

This study provides further evidence that atrioventricular pacing is better than ventricular demand pacing and should be considered in all suitable patients.

References

1 Geddes JS. "Physiological" pacing. *Br Heart J* 1983;50:109–11.

2 Kruse I, Arnman K, Conradson TB, Ryden L. A comparison of the acute and long-term hemodynamic effects of ventricular inhibited and atrial synchronous ventricular inhibited pacing. *Circulation* 1982;65:846–55.

3 Perrins EJ, Morley CA, Chan SL, Sutton R. Randomised controlled trial of physiological and ventricular pacing. *Br Heart J* 1983;50:112–7.

4 Kristensson BE, Arnman K, Smedgard P, Ryden L. Physiological versus single rate ventricular pacing: a double blind cross-over study. *PACE* 1985;8:73–84.

5 Stone JM, Bhakta RD, Lutgen J. Dual chamber sequential pacing management of sinus node dysfunction: advantages over single chamber pacing. *Am Heart J* 1982;104:1319–27.

6 Alicandri C, Fouad FM, Tarazi RC, Castle L, Morant V. Three cases of hypotension and syncope with ventricular pacing. Possible role of atrial reflexes. *Am J Cardiol* 1978;42:137–42.

7 Jones RI, Cashman PMM, Hornung RS, Prince H, Bassein L, Raftery EB. Ambulatory blood pressure and assessment of pacemaker function. *Br Heart J* 1986;55:462–8.

8 Morley CA, Perrins EJ, Grant P, Chan SL, McBrien DJ, Sutton R. Carotid sinus syncope treated by pacing. Analysis of persistent symptoms and role of atrioventricular sequential pacing. *Br Heart J* 1982;47:411–8.

9 Boon NA, Frew AJ, Cobbe SM. An intra-patient comparison of ambulatory blood pressure during chronic DDD and VVI pacing [Abstract]. *Br Heart J* 1986;55:508.

10 Littler WA, Honour AJ, Sleight P, Stott FD. Continuous recording of direct arterial pressure and electrocardiogram in unrestricted man. *Br Med J* 1972;iii:76–8.

11 Rowlands DB, Stallard TJ, Littler WA. Continuous ambulatory monitoring of blood pressure and assessment of cardiovascular reflexes in the elderly hypertensive. *J Hypertens* 1984;2:615–22.

12 Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J* 1973;i:507–10.

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Is ventricular arrhythmia in repaired tetralogy of Fallot an effect of operation or a consequence of the course of the disease?

A prospective study

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SUMMARY Ventricular arrhythmia is common after repair of tetralogy of Fallot. Such arrhythmia could be caused by damage at surgical repair or it could be part of the course of the disease. Fifty patients, 32 aged 1–7 years and 18 aged 13–43 years at surgical repair, underwent 24 hour electrocardiographic monitoring before and 2–75 (mean 44) months after repair. Before operation none of the younger group had appreciable ventricular arrhythmia, whereas ventricular arrhythmia was already present in eight (45%) of 18 patients in the older group. At follow up ventricular arrhythmia was present in four patients from the younger group and seven from the older group. Three of these four younger patients had had insertion of a conduit from the right ventricle to the pulmonary artery or reoperation. Six of the seven older patients had had appreciable ventricular arrhythmia before operation. New ventricular arrhythmia developed in only two (5%) of the 43 patients who had uncomplicated repair of tetralogy of Fallot.

Thus the high frequency of ventricular arrhythmia after repair of tetralogy of Fallot cannot be attributed to the effect of operation alone because in the majority of patients it was already present before operation. Preoperative ventricular arrhythmia occurred almost exclusively in older patients; this suggests that early surgery may reduce the occurrence of this late complication.

Ventricular arrhythmia is well recognised after repair of tetralogy of Fallot and has been suggested as a cause of late sudden death.[1 2] Factors which predispose to the high incidence of ventricular arrhythmia in patients after operation remain controversial. Residual haemodynamic abnormalities after surgery, such as right ventricular systolic and diastolic hypertension,[3] increased right ventricular dimension,[4] and diminished right ventricular ejection fraction,[5] have been regarded as important. In a previous study, however, the frequency of ventricular arrhythmia was already high in older patients before repair of tetralogy of Fallot.[6] This has implications for strategies aimed at reducing the occurrence of this late complication.

We have therefore performed a prospective study to determine the relative important of preoperative, operative, and postoperative factors in the genesis of ventricular arrhythmia. This aimed to test the hypothesis that the presence of ventricular arrhythmia after surgical repair of tetralogy of Fallot depends as much on the natural cause of the disease and preoperative status as on the direct effect of the operation itself.

Patients and methods

PATIENTS

We studied 55 consecutive patients undergoing surgery for classic tetralogy of Fallot. There were

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two groups. Group A consisted of 35 children, aged 1·2–7·7 (median 4·3) years at repair, admitted to the Hospital for Sick Children, London. Group B consisted of 20 older patients, aged 13–43 (median 28) years, who underwent repair of tetralogy of Fallot in Turin.

Previous palliative surgery had been performed in 20 patients from group A and in 17 patients from group B (Blalock-Taussig shunt 29, Potts shunt 3, Waterston shunt 1, Brock procedure 4). Repair involved right ventriculotomy in all patients except for one in group B whose repair was performed through the tricuspid and pulmonary valves. The right ventricular outflow tract procedure consisted of an infundibulectomy, usually together with an outflow tract or transannular patch, except for three patients in group A who required right ventricle to pulmonary artery conduits because of an aberrant coronary artery. Reoperation was necessary in four patients, all from group A, for closure of residual ventricular septal defect or pulmonary valve replacement or both.

All patients underwent 24 hour electrocardiographic monitoring before repair. There were three operative deaths in group A. Follow up electrocardiographic monitoring was performed in all 32 remaining patients 8–75 (median 54) months after repair. There were no operative deaths in group B and follow up electrocardiographic monitoring was performed 2–42 (median 30) months after repair in all except two patients who were symptom free and declined investigation. There were no late cardiac deaths; the only death occurred in a previously symptom free group B patient after postpartum haemorrhage.

ELECTROCARDIOGRAPHIC MONITORING

Electrocardiographic monitoring was performed with Oxford Medilog or Avionics cassette recorders with bipolar CM1 and CM5 leads. The tapes were analysed with an Oxford Medilog or Avionics high speed analyser. A modification of Lown criteria,[7] based on frequency and complexity of ventricular arrhythmia, was used for all the recordings: grade 0 = no ventricular extrasystoles; grade I = ventricular extrasystoles with peak hourly rate < 30; grade II = > 30 uniform ventricular extrasystoles in any hour; grade III = couplets (two consecutive ventricular extrasystoles), or multiform ventricular extrasystoles with peak hourly rate > 30; grade IV = ventricular tachycardia (three or more consecutive extrasystoles with mean rate > 110 beats/min).

Standard 12 lead electrocardiograms were used to assess the mean frontal plane QRS axis and intraventricular conduction abnormality.

STATISTICAL ANALYSIS

The incidence of ventricular arrhythmia (grade II or greater) between groups A and B and within groups, before and after surgery, was compared by Fisher's exact test. Differences were regarded as significant if the probability of a chance occurrence was < 0·05.

Results

PREOPERATIVE ELECTROCARDIOGRAPHIC MONITORING

Before surgical repair none of the younger patients (group A) had appreciable ventricular arrhythmia (grade II or greater). All except three had uninterrupted sinus rhythm, and the remainder had a total of < 10 uniform ventricular extrasystoles during the 24 hour period. In contrast, eight (45%) of the 18 older patients (group B) already had ventricular arrhythmia of grade II or greater during preoperative ambulatory monitoring; this was a significantly higher incidence than in the younger patients of group A (p = 0·0009). These included five (28%) patients with frequent complex ventricular arrhythmia (grade III) (fig 1).

FOLLOW UP ELECTROCARDIOGRAPHIC MONITORING

At follow up after repair four (13%) of the 32 patients in group A had ventricular arrhythmia of grade II or greater (fig 2). The occurrence of new ventricular arrhythmia in the subgroup of seven patients with conduit insertion or repeat surgery was significantly higher than in the patients who had

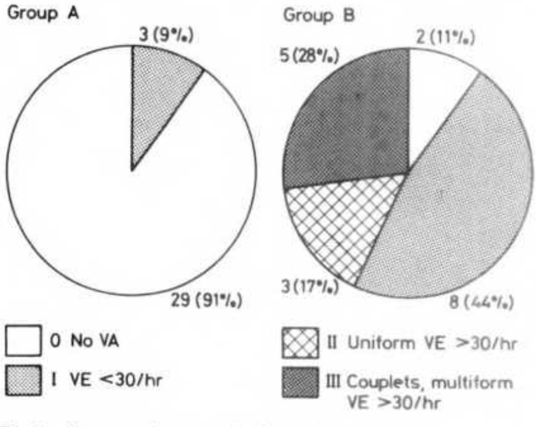

Fig 1 *Preoperative ventricular arrhythmia on electrocardiographic monitoring in the two groups of patients. In group A (younger patients at repair) the frequency and grade of ventricular arrhythmia were low. In contrast 45% of group B (older patients at repair) had frequent or complex ventricular arrhythmia. VA, ventricular arrhythmia; VE, ventricular extrasystole.*

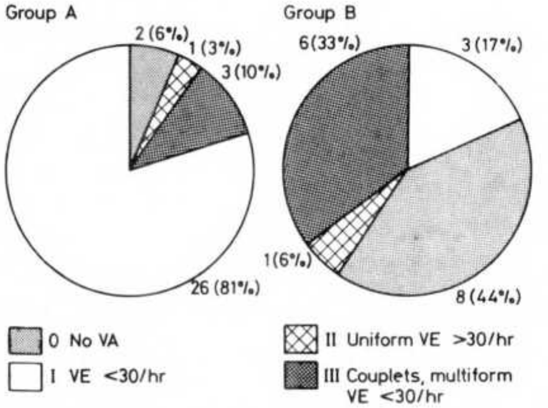

Fig 2 *Ventricular arrhythmia on follow up electrocardiographic monitoring. The frequency of ventricular arrhythmia in group A patients remained low while the high incidence of ventricular arrhythmia in group B patients noted before operations persisted. See legend to fig 1 for abbreviations.*

uncomplicated repair (3/7 *vs* 1/25, p = 0·02) (table).

At follow up evaluation seven (39%) of the 18 older patients (group B) had ventricular arrhythmia of grade II or greater (fig 2). Ventricular arrhythmia of a similar grade had been present in six of these during preoperative monitoring. Thus only one patient developed ventricular arrhythmia of grade II or greater that had not been detected before surgery (fig 3). Because most ventricular arrhythmia was present before operation, there was no relation between postoperative ventricular arrhythmia and the type of surgery in this older group, unlike group A. No patient had ventricular tachycardia.

Right bundle branch block was present in 45 (90%) of the 50 patients after surgery, with additional left axis deviation (frontal plane QRS axis > −30°) in five (10%). There was no relation between ventricular arrhythmia detected by electrocardiographic monitoring and these conduction defects on the 12 lead electrocardiogram.

Table *Relation of surgical procedures and postoperative ventricular arrhythmia in group A (younger patients at repair).*

	No	*Ventricular arrhythmia*		
Simple repair	25	1	(4%)	p = 0·02
RV PA conduit	3	1	(43%)	
Reoperation: (VSD, VSD + PVR, PVR)	4	2		
Total	32	4		

PA, pulmonary artery; PVR, pulmonary valve replacement; RV, right ventricle; VSD, ventricular septal defect.

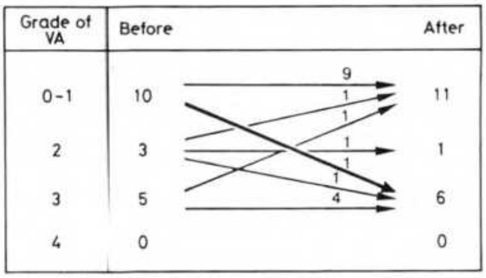

Fig 3 *Comparison of grade of ventricular arrhythmia (VA) in group B before and after operation. Only one patient had appreciable ventricular arrhythmia after repair that had not been noted on preoperative monitoring. See figs 1 and 2 for ventricular arrhythmia grading.*

The overall occurrence of postoperative ventricular arrhythmia for groups A and B together was 22% (11/50). Of these, only two patients had new ventricular arrhythmia after uncomplicated surgical repair. The remainder had either insertion of a conduit from the right ventricle to the pulmonary artery (one patient), reoperation (two patients), or had similar ventricular arrhythmia already present before operation.

Discussion

Despite the fact that ventricular arrhythmia is widely recognised after repair of tetralogy of Fallot, neither the important precipitating factors nor specific indications for arrhythmia suppression have been adequately defined.

Some groups have reported an association between the presence of ventricular arrhythmia and inadequate repair of tetralogy of Fallot. Garson *et al* noted that about 25% of patients with right ventricular systolic pressure >60 mm Hg demonstrated postoperative ventricular arrhythmia, compared with 8% of those with a right ventricular systolic pressure <40 mm Hg.[3] Webb Kavey *et al* failed to demonstrate a similar haemodynamic correlation despite finding ventricular arrhythmia in 42% of 72 patients.[8] In the group of patients with ventricular arrhythmia, however, they found a more subtle haemodynamic impairment on radionuclide and cross sectional echocardiographic examination.[9]

These retrospective studies, however, included many older patients operated on in the early years of cardiopulmonary bypass, and they did not measure the occurrence of ventricular arrhythmia before surgical repair. In the only previous study to do so, half the 24 patients aged ≥8 years had ventricular arrhythmia before repair—similar to those found in postoperative recordings.[6] This suggested that the natural course of the disease and the preoperative state of the right ventricle might be at least as important as the direct effect of operation on the genesis of postoperative ventricular arrhythmia. Our prospective study supports this hypothesis; most of our patients with ventricular arrhythmia after repair of tetralogy of Fallot had this abnormality before operation. Only two (5%) of the 43 patients with uncomplicated repair developed new ventricular arrhythmia after operation.

Why does ventricular arrhythmia occur in patients with tetralogy of Fallot, even before repair? The likelihood of its developing appears to increase with age. This is supported by both the relation between older age at repair and symptoms of arrhythmia[10] and by the results of electrocardiographic monitoring.[6] The anatomical substrate for this may be the degree of right ventricular myocardial fibrosis. In older patients undergoing repair for tetralogy of Fallot pathological studies have demonstrated extensive right ventricular fibrosis which is not present in younger children.[11,12] Similar right ventricular fibrosis was noted at necropsy in patients who died suddenly late after repair of tetralogy of Fallot.[13] Electrophysiological studies with endocardial mapping have demonstrated fractionated depolarisation at multiple sites in the right ventricle in patients after repair of tetralogy of Fallot that correlated with ventricular arrhythmia on electrocardiographic monitoring. This suggests a widespread abnormality of right ventricular electrical activity rather than a central conduction defect specifically related to a direct effect of surgical repair.[14]

Surgical repair clearly may have an effect in predisposing to ventricular arrhythmia. Sustained ventricular tachycardia has been mapped to the site of incision in the right ventricular outflow tract[15] and fractionated depolarisation has been recorded from the ventricular septum[16]—presumably this is related to repair of the ventricular septal defect. In our study there were five patients who did not have ventricular arrhythmia before operation but who had appreciable ventricular arrhythmia at follow up. It is notable, however, that most of them had extensive or repeated surgery likely to produce more right ventricular scarring than straightforward repair of tetralogy of Fallot.

The two groups in this study were managed at different institutions. Because we were investigating intrapatient differences, however, this does not compromise our conclusions. Furthermore, our results indicate that the operation itself had little direct effect.

As this is a prospective study, follow up is necessarily shorter than in previous retrospective studies. It could be argued that with time ventricular arrhythmia will develop even in patients operated on at a younger age. Indeed, Garson *et al* consider that patients with early repair "have not lived long enough to develop premature ventricular complexes." They believe that this explains the relation they found between the occurrence of postoperative ventricular extrasystoles and older age at repair.[3] Nevertheless, from our previous analysis of 85 patients we could find no significant relation between ventricular arrhythmia and duration of follow up[6] when this was analysed independently of age of surgical repair. This question will need to be examined in prospective studies, such as this one, with a longer follow up.

We did not attempt to define the indications for antiarrhythmic treatment in patients with ventricular arrhythmia after repair of tetralogy of Fallot, which remain controversial. There have been no late cardiac deaths among this study group to date and most patients are symptom free. In a separate six year prospective study the prognostic significance of asymptomatic ventricular arrhythmia has been low.[17]

This study highlights the importance of the natural course of ventricular arrhythmia in tetralogy of Fallot. Preoperative abnormalities of the right ventricular myocardium at operation seem to be as important as any direct effect of operation in predisposing to subsequent ventricular arrhythmia. Preoperative ventricular arrhythmia occurred exclusively in the older patients. It is thus tempting to speculate that earlier surgical repair, which has become standard, may reduce the occurrence of this late complication.

References

1 Deanfield JE, McKenna WJ, Hallidie-Smith KA. Detection of late arrhythmia and conduction disturbance after correction of tetralogy of Fallot. *Br Heart J* 1980;**44**:248–53.

2 Gillette PC, Yeoman MA, Mullins CE, McNamara DG. Sudden death after repair of tetralogy of Fallot. Electrocardiographic and electrophysiologic abnormalities. *Circulation* 1977;**56**:566–71.

3 Garson A Jr, Randall DC, Gillette PC, *et al.* Prevention of sudden death after repair of tetralogy of Fallot: treatment of ventricular arrhythmias. *J Am Coll Cardiol* 1985;**6**:221–7.

4 Rosing DR, Borer JS, Kent KM, *et al.* Long-term hemodynamic and electrocardiographic assessment following operative repair of tetralogy of Fallot. *Circulation* 1978;**58**(suppl I):209–17.

5 Kobayashi J, Hirose H, Nakano S, Matsuda H, Shirakura R, Kawashima Y. Ambulatory electrocardiographic study of the frequency and cause of ventricular arrhythmia after correction of tetralogy of

Fallot. *Am J Cardiol* 1984;54:1310–3.

6 Deanfield JE, McKenna WJ, Presbitero P, England D, Graham GR, Hallidie-Smith K. Ventricular arrhythmia in unrepaired and repaired tetralogy of Fallot. Relation to age, timing of repair, and haemodynamic status. *Br Heart J* 1984;52:77–81.

7 Ryan M, Lown B, Horn H. Comparison of ventricular ectopic activity during 24-hour monitoring and exercise testing in patients with coronary heart disease. *N Engl J Med* 1975;292:224–9.

8 Webb Kavey R-E, Blackman MS, Sondheimer HM. Incidence and severity of chronic ventricular dysrhythmias after repair of tetralogy of Fallot. *Am Heart J* 1982;103:342–50.

9 Webb Kavey R-E, Thomas FD, Byrum CJ, Blackman MS, Sondheimer HM, Bove EL. Ventricular arrhythmia and biventricular dysfunction after repair of tetralogy of Fallot. *J Am Coll Cardiol* 1984; 4:126–31.

10 Katz NM, Blackstone EH, Kirklin JW, Pacifico AD, Bargeron LM Jr. Late survival and symptoms of repair of tetralogy of Fallot. *Circulation* 1982; 65:403–10.

11 Jones M, Ferrans VJ. Myocardial degeneration in congenital heart disease. Comparison of morphologic findings in young and old patients with congenital heart disease associated with muscular obstruction to right ventricular outflow. *Am J Cardiol* 1977; 39:1051–63.

12 Meurs-van Woezik H, Brink HS, Essed CE, Debets T, Klein HW, Krediet P. Myocardial fibrosis in tetralogy of Fallot [Abstract]. In: Doyle EF, Engle MA, Gersony WM, Rashkind WJ, Talner NS, eds. *Second world congress of pediatric cardiology*. New York: Springer-Verlag, 1985:145.

13 Deanfield JE, Ho S-Y, Anderson RH, McKenna WJ, Allwork SP, Hallidie-Smith KA. Late sudden death after repair of tetralogy of Fallot: a clinico-pathologic study. *Circulation* 1983;67:626–31.

14 Deanfield J, McKenna W, Rowland E. Local abnormalities of right ventricular depolarization after repair of tetralogy of Fallot: a basis for ventricular arrhythmia. *Am J Cardiol* 1985;55:522–5.

15 Horowitz LN, Vetter VL, Harken AH, Josephson ME. Electrophysiologic characteristics of sustained ventricular tachycardia occurring after repair of tetralogy of Fallot. *Am J Cardiol* 1980;46:446–52.

16 Kugler JD, Pinsky WW, Cheatham JP, Hofschire PJ, Morring PK, Fleming WH. Sustained ventricular tachycardia after repair of tetralogy of Fallot: electrophysiologic findings. *Am J Cardiol* 1983;51:1137–43.

17 Deanfield J, Franklin R, McKenna WJ, Dickie S, Gersony W, Hallidie-Smith K. Prognostic significance of ventricular arrhythmia after repair of tetralogy of Fallot: a prospective study. In: Doyle EF, Engle MA, Gersony WM, Rashkind WJ, Talner NS, eds. *Pediatric cardiology*. New York: Springer-Verlag, 1986: 467–8.

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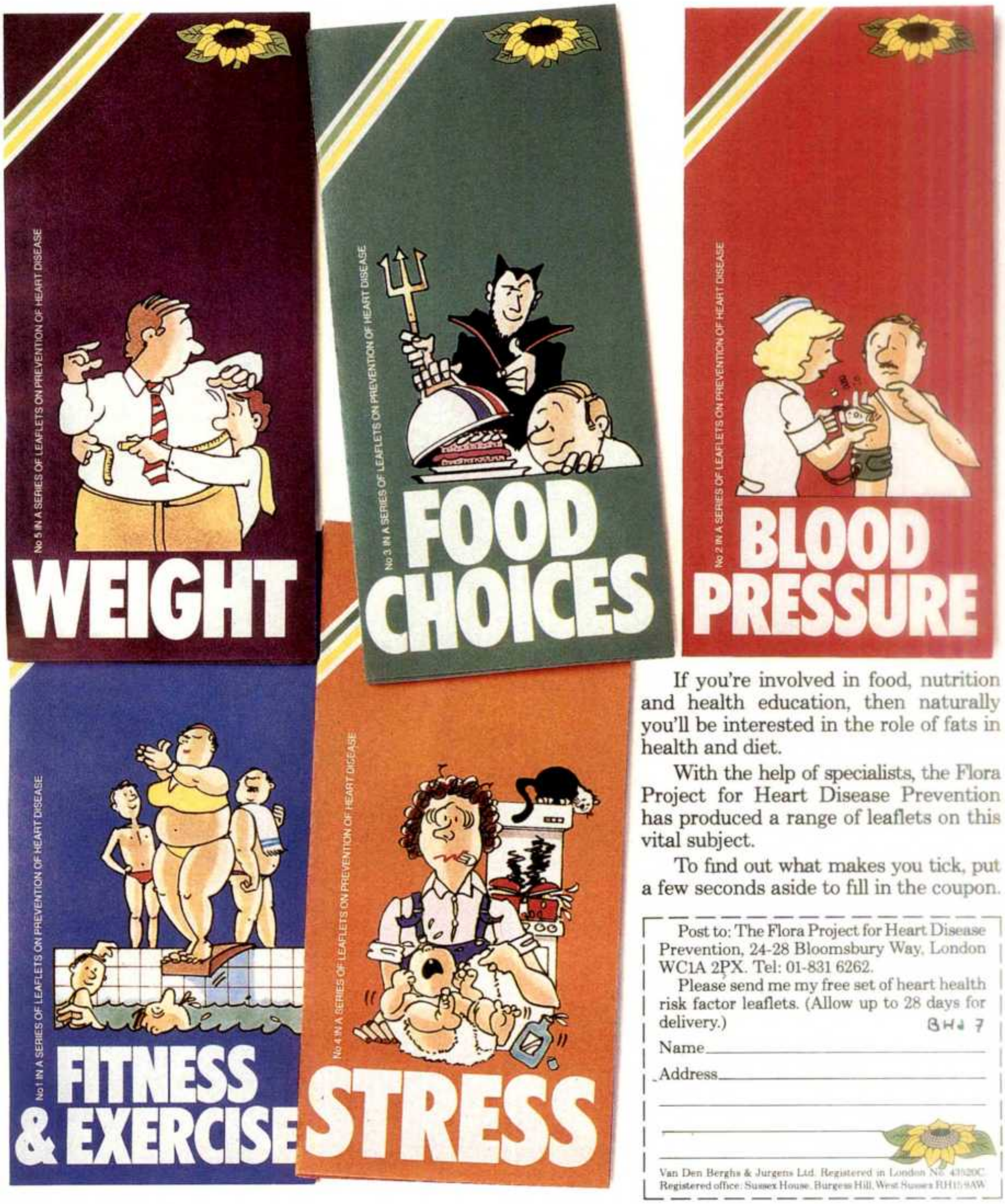
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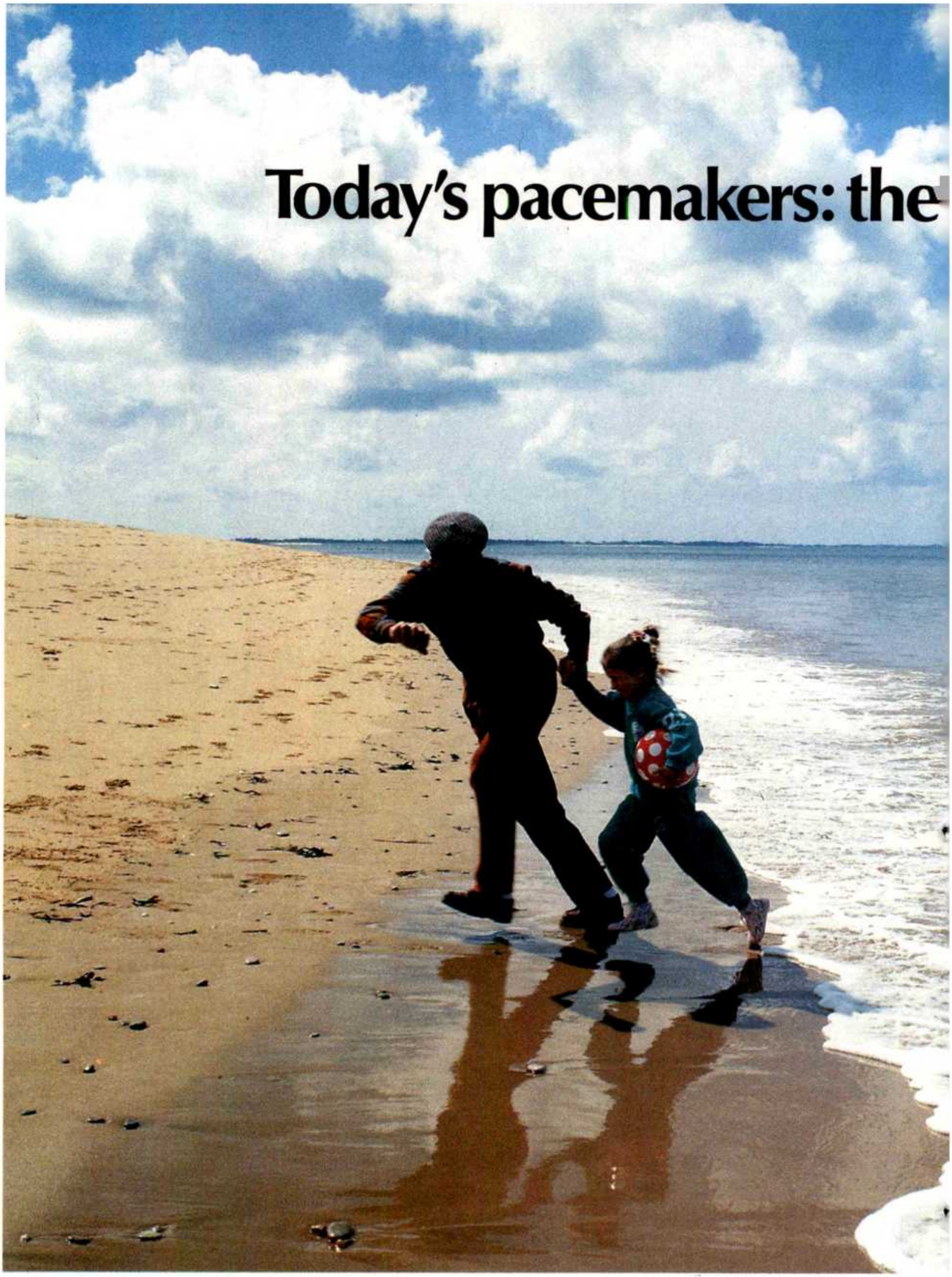

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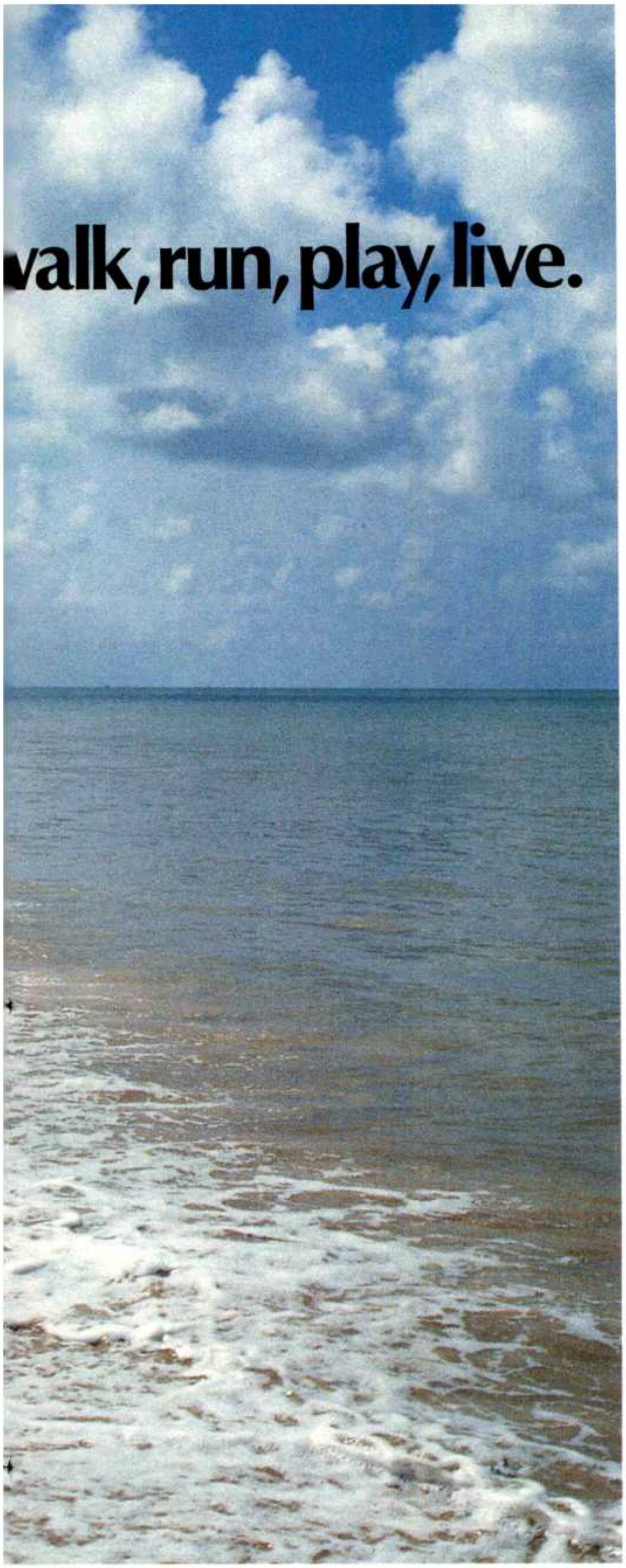

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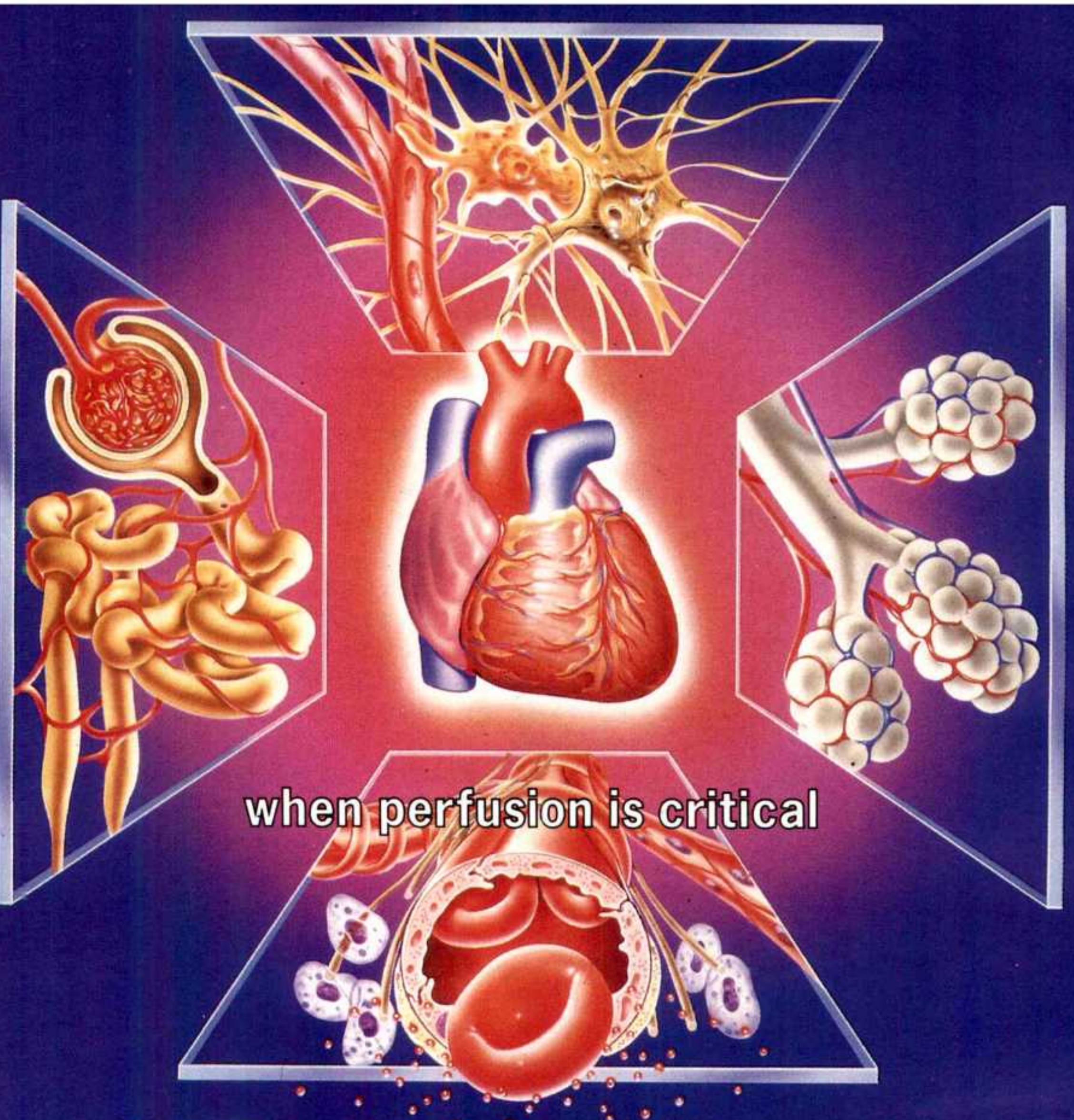

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Br Heart J 1987;58:45–51

Detection of aortic dissection by transoesophageal echocardiography

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SUMMARY The diagnostic value of a combination of transoesophageal and transthoracic echocardiography was evaluated in 21 patients with dissection of the aorta. The results were compared with those of computed tomography, aortography, and with findings at operation or necropsy or both. Transthoracic echocardiography identified three of the four patients with type I dissection, two of the five patients with type II dissection, and one of the 12 patients with type III dissection. When transoesophageal echocardiography was used as well the degree of aortic dissection was identified correctly in all 21 patients. In one patient with type I and in eight patients with type III dissection spontaneous echocardiographic contrast with a mural thrombus within the false lumen could be detected. Computed tomography was unable to demonstrate an intimal flap in one of two patients studied with type I dissection, in two of three patients with type II dissection, and in one of nine patients with type III dissection. Aortography was negative in one of two patients studied with type I dissection, two of four patients with type II dissection, and in one of eight patients with type III dissection.

The whole thoracic aorta can be imaged by a combination of transthoracic and transoesophageal echocardiography. The addition of transoesophageal echocardiography to transthoracic echocardiography improves the recognition of aortic dissection. Furthermore, this examination can be performed at the bedside and the findings can be used as a basis for treatment.

Echocardiography is a useful method for detecting aortic dissection.[1–4] The aortic arch can be imaged from the suprasternal approach.[5 6] The descending part of the thoracic aorta can be imaged behind the heart in the left parasternal view.[7 8] Thus almost the whole thoracic aorta can be visualised, however, there are difficulties in imaging the dissections in the distal part of the aorta. The whole aorta can be imaged in only about 70% of obese patients and those with pulmonary emphysema.[4] Cross sectional transoesophageal echocardiography, introduced by Hanrath *et al*,[9] has opened up a new approach to both the heart[10–12] and the aorta[13] making it possible to produce cross sectional images of the descending aorta in multiple scanning planes.[13]

We have evaluated the accuracy of transoesophageal cross sectional echocardiography for the diagnosis of aortic dissection and we have compared its effectiveness with transthoracic echocardiography, computed tomography, and aortography.

Patients and methods

The ascending aorta was imaged by transthoracic echocardiography in the long and short axes in different planes from the precordial, apical, suprasternal, and subcostal approaches.[5–8] Over a 36 month period 13 700 transthoracic echocardiograms were obtained. Of these patients, 800 were also examined by transoesophageal echocardiography because disease of the left and right atria and mitral and aortic values was suspected. Aortic dissection was detected by transoesophageal echocardiography in 21 patients. These patients, in whom the aortic

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dissection was also shown by alternative techniques, form the basis of the study. In 25 (3%) of the 800 patients transoesophageal echocardiography was not possible because the patient could not tolerate the gastroscopic procedure. Side effects were seen in two patients. One suffered from a severe attack of asthma and one showed a transient grade III atrioventricular block during introduction of the echoscope. When necessary patients were given intravenous atropine (0·5 mg) before the procedure. All patients gave their informed consent and fasted for at least four hours before the procedure. Each patient's history was studied carefully to exclude a diverticulum of the oesophagus. All echocardiographic examinations were performed with a V-3400 R or CV 60 (Diasonics, Palo Alto) phased array sector scanner. A 2·25 MHz transducer was used for the transthoracic studies. Transoesophageal echocardiography was performed with a 3·5 MHz transducer array of 48 elements fitted to the distal end of a conventional 12 mm endoscope.[9] Echocardiographic readings were stored on a video tape recorder.

The echoscope was introduced into the oesophagus up to 40 cm distal to the patient's teeth. When the transducer was directed anteriorly the aortic valve and aortic root could be imaged as previously described.[9] More distal parts of the ascending aorta and aortic arch could not be imaged from this point except in patients with aortic ectasia.

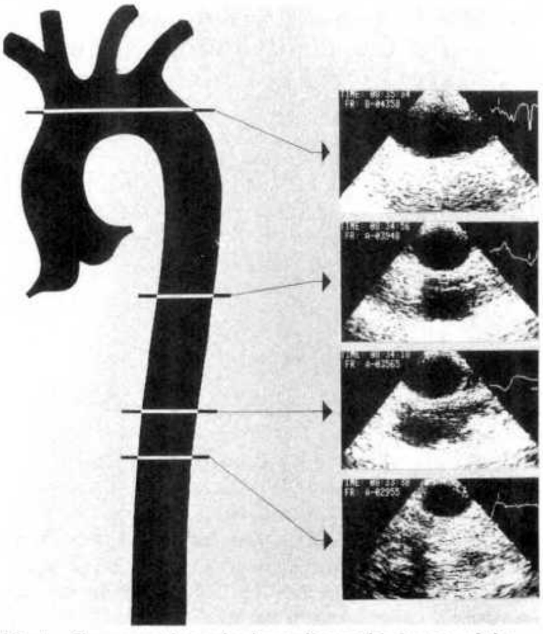

Fig 1 *Transoesophageal echocardiographic images of the thoracic aorta in a normal subject.*

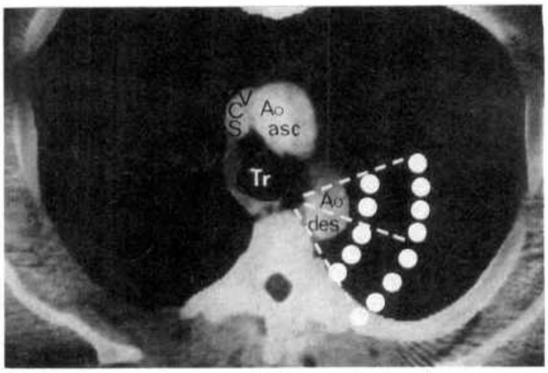

Fig 2 *Computed tomographic image showing the sector scan for transoesophageal echocardiogram imaging of the descending aorta. VCS, superior vena cava; Tr, trachea; Ao des, descending aorta; Ao asc, ascending aorta.*

By rotating the transducer posteriorly, the descending part of the thoracic aorta was visualised (fig 1). The sector scans from the echoscope are shown on a computed tomogram at the descending aorta (fig 2). By moving the echoscope within the oesophagus multiple cross sectional images could be obtained (fig 2). At a depth of 20–22 cm the descending aortic arch could be visualised (fig 3). Normal values for the aortic diameter were determined in 12 controls. Mean (SD) values are given.

Aortography (Cardioscop U, Siemens) and computed tomographic studies (scan time 4 s; Somatom, Siemens) were also performed so that the accuracy of transoesophageal echocardiography could be compared with standard methods.

Echocardiographically and angiographically an aneurysm was defined as a localised dilatation of a portion of the thoracic aorta. Diagnosis of a dis-

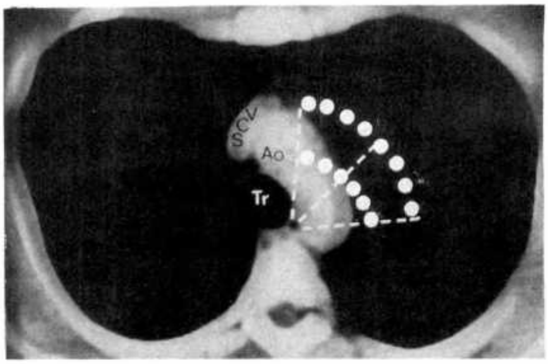

Fig 3 *Computed tomogram showing the sector scan for transoesophageal echocardiogram imaging of the aortic arch. Because of the interposition trachea (Tr) the ascending aorta cannot be imaged from this point. Ao, aorta; VCS, superior vena cava.*

section was based on the recognition of an intimal tear, identified as a linear structure that changed position during the cardiac cycle. A dissection was detected in 21 patients. The extent of the dissection was defined according to the DeBakey classification[14]: type I dissection begins in the ascending aorta and extends beyond the arch, type II dissection is confined to the ascending aorta, and type III dissection originates in the descending thoracic aorta and continues distally.

STATISTICAL ANALYSIS

Mean (SD) values are given. Linear regression analysis was performed and correlation coefficients (r) and regression equations are given for comparison of aortic diameters measured by computed tomography and transoesophageal echocardiography.

Results

Four patients had type 1 aortic dissection, five had type II, and twelve had type III. Sixteen patients had hypertension and two had Marfan syndrome; in three patients the aetiology of dissection was unknown. There was aortic regurgitation in all patients with type I dissection and in four of five patients with type II dissection. Table 1 shows the results of transthoracic and transoesophageal echocardiography, computed tomography, and angiography, and the findings at operation and necropsy. Transoesophageal echocardiography detected dissection in all patients in whom it was shown by alternative techniques. Table 2 gives the diameters of the different parts of the aorta measured by transoesophageal echocardiography and computed tomography. Figure 4 shows a typical example of aortic dissection type I in which there was an intimal flap within the ascending aorta, the aortic arch, and the descending aorta. In one young woman (patient 3) an entry tear 2 cm distal to the aortic valve was demonstrated by transoesophageal echocardiography and emergency operation was performed without further diagnostic procedures. In other woman (patient 4) operation was done after additional coronary angiography which demonstrated a stenosis in the distal part of the left anterior

Table 1 *Clinical data and diagnostic results of 21 patients with aortic dissection*

Case	*Age/sex*	*Type of dissection*	*AI*	*TOE*	*TTE*	*CT*	*Angiography*	*Surgery*	*Necropsy*
1	28 M	I	+	+	–	–	–	+	0
2	69 F	I	+	+	+	+	0	+	0
3	36 F	I	+	+	+	0	0	+	0
4	68 F	I	+	+ (thrombus, SEC)	+	0	+	+	0
5	30 F	II	+	+	–	0	–	+	0
6	77 F	II	+	+	+	–	0	0	0
7	71 F	II	+	+ (thrombus)	+	0	–	0	+
8	36 F	II	+	+	–	–	+	0	0
9	55 F	II	–	+	–	+ (MRT)	+	+	0
10	52 M	III	–	+ (thrombus, SEC)	–	+ (thrombus)	+	0	0
11	72 M	III	–	+	+	+	0	0	+
12	64 F	III	–	+ (thrombus, SEC)	– (thrombus)	0	+	0	+
13	69 M	III	–	+ (thrombus, SEC)	–	+	+	0	0
14	76 M	III	–	+ (thrombus, SEC)	–	+ (thrombus)	0	0	0
15	71 M	III	–	+ (SEC)	–	+ (thrombus)	0	0	0
16	66 F	III	–	+ (thrombus, SEC)	–	0	+ (thrombus)	+	0
17	64 F	III	+	+ (thrombus, SEC)	–	– (thrombus)	+	0	0
18	79 F	III	–	+ (thrombus, SEC)	–	0	+	0	0
19	63 M	III	–	+ (thrombus)	–	+	+	+	0
20	45 M	III	–	+ (thrombus)	–	+ (thrombus)	–	0	0
21	72 M	III	–	+ (thrombus)	–	+ (thrombus)	0	0	0

AI, aortic insufficiency; +, confirmed; –, no diagnosis by transthoracic and transoesophageal echocardiography (TTE/TOE), computed tomography (CT), aortic angiography (angio), surgery, or necropsy; 0, no data; SEC, spontaneous echocardiographic contrast; MRT, magnetic resonance tomography.

Table 2 *Transoesophageal echocardiographic (TOE) and computed tomographic (CT) diameters (D) of the ascending aorta, aortic arch, and descending aorta*

		Aortic diameter (mm)					
		Ascending aorta		*Aortic arch*		*Descending aorta*	
Case	*Type of dissection*	*TOE*	*CT*	*TOE*	*CT*	*TOE*	*CT*
1	I	63	47	26	30	25	30
2	I	45	50	33	36	34	38
3	I	37	—	25	—	27	—
4	I	38	—	33	—	35	—
5	II	61	—	28	—	25	—
6	II	68	70	42	46	48	54
7	II	55	—	33	—	28	—
8	II	45	52	32	30	25	32
9	II	50	—	30	—	22	—
10	III	35	35	33	33	45	50
11	III	45	50	45	50	35	40
12	III	35	—	33	—	58	—
13	III	36	33	33	35	38	45
14	III	35	32	35	33	60	75
15	III	35	—	32	—	35	—
16	III	40	—	70	—	32	—
17	III	64	61	40	40	54	58
18	III	34	—	28	—	30	—
19	III	44	46	50	48	57	61
20	III	36	36	33	34	36	39
21	III	35	35	30	28	38	35
Mean (SD)		45 (11)	46 (12)	35 (10)	37 (7)	37 (12)	46 (14)
		$D_{CT} = 0{\cdot}85 D_{TEE} + 6{\cdot}3$		$D_{CT} = 1{\cdot}0\ D_{TEE} + 0{\cdot}57$		$D_{CT} = 1{\cdot}1 D_{TEE} + 0{\cdot}45$	
		$r = 0{\cdot}88$		$r = 0{\cdot}93$		$r = 0{\cdot}96$	
Normal values		<35 mm		<30 mm		<25 mm	

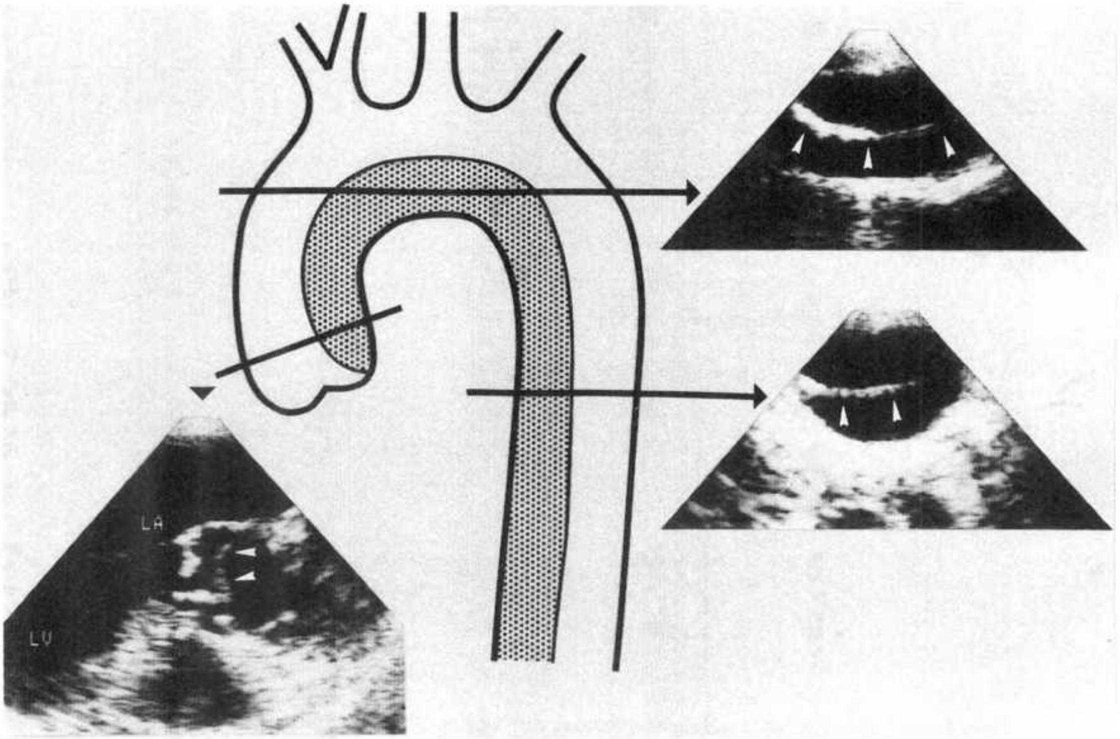

Fig 4 *Typical example of a type I dissection (patient 2) showing the intimal flap (↓) in the ascending aorta, the aortic arch, and the descending aorta. LA, left atrium; LV, left ventricle.*

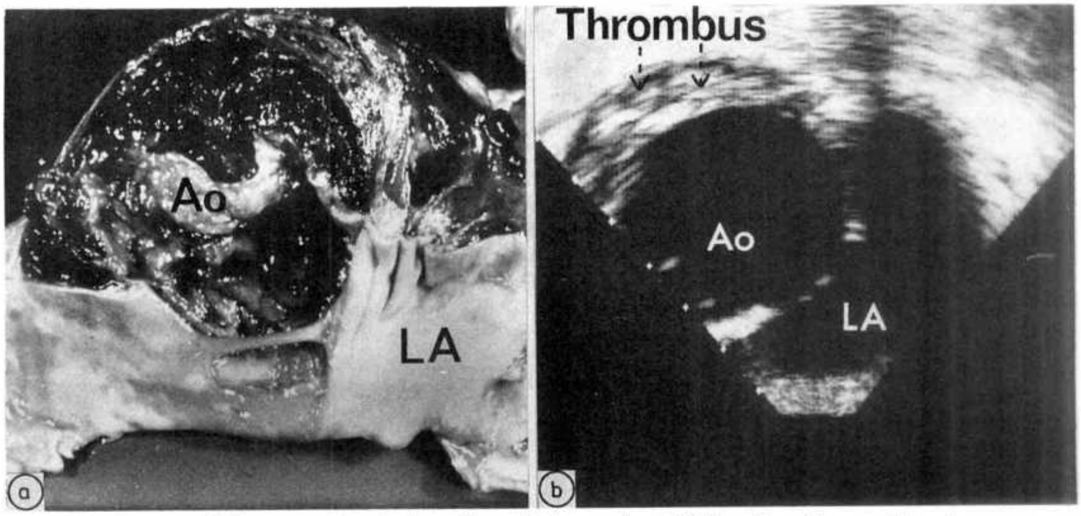

Fig 5 *Section (a) and (b) cross sectional echocardiographic image of type II dissection with mural thrombus formation within the false lumen. To assist comparison the echocardiographic image has been turned upside down. Ao, aorta; LA, left atrium.*

descending coronary artery. Transoesophageal echocardiography demonstrated the entry tear of the dissection in this case too.

A type II dissection was found by transoesophageal echocardiography in five patients, and an intimal flap showing movement parallel to the aortic wall was clearly demonstrated within the ascending part of the aorta in all five. The aorta was dilated in all five cases. Aortography was positive in only two of four of these patients. Diagnosis was confirmed at operation in two patients and by necropsy in another patient (fig 5). In this last patient the false lumen was filled with a thrombus, which explains the negative result at aortography.

A type III dissection was seen in 12 patients by transoesophageal echocardiography (fig 6). Computed tomography was positive in eight of nine of these patients. Aortography was performed in eight patients and was positive in seven. In eight of the 12 patients spontaneous echocardiographic contrast was seen within the aorta. There were circulating flow patterns and thrombus formation in that part of the aorta in which the spontaneous echocardiographic contrast was most obvious (fig 6). The starting point of the aortic dissection could be demonstrated in all 12 patients. In two patients with type III dissection the intimal entry tear could also be visualised.

Discussion

In up to 18% of patients aortic dissection may be missed at chest *x* ray or may cause non-specific signs that do not distinguish the abnormality from aneurysmal dilatation or tortuosity and elongation of the aorta without dissection.[15] Thus reliable non-invasive techniques are needed for immediate and accurate diagnosis in seriously ill patients with chest pain.[16] Computed tomography and echocardio-

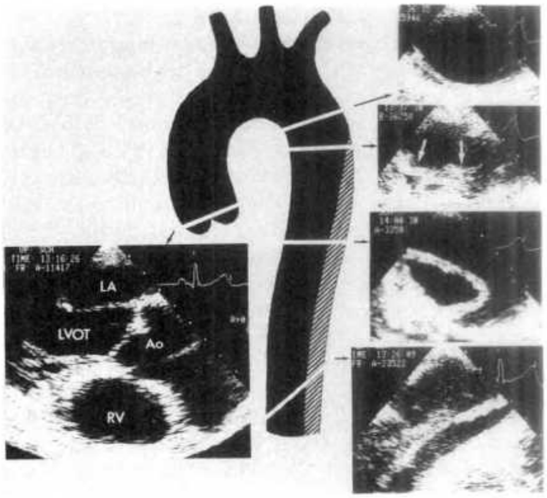

Fig 6 *Transoesophageal echocardiogram showing type III aortic dissection and spontaneous echocardiographic contrast within the false lumen. Mural thrombus formation was seen in the part with the densest spontaneous echocardiographic contrast (↓). LA, left atrium; LVOT, left ventricle outflow tract; RV, right ventricle; Ao, aorta.*

graphy are regarded as the most successful approaches. The first report of the diagnosis of aortic dissection by computed tomography[17] was confirmed by others.[18,19] Detection of an intimal flap is probably the most specific sign. After a bolus injection of contrast medium true and false lumens were visualised in about 50% of patients in whom the aortic diameter was increased.[20–24] We had similar success with type I and II dissection. Type III dissection was successfully detected in 90% of patients. The strong movement of the intimal flap during the cardiac cycle may explain the negative results. The scanning time of 4 s for computed tomography cannot give a sharp image of the membrane in all patients.

M mode echocardiography can detect enlargement of the aortic root, widening of the anterior or posterior aortic wall, and the presence of intimal flaps.[1–3,25–28] Some workers have used scanning from multiple anatomical sites to image the whole of the thoracic aorta by cross sectional echocardiography[5,8,29] and to distinguish the type and extent of dissection.[29–32] Detection of distal dissection of the thoracic aorta was difficult.[8,29] It was successful in only about 70% of cases.[4] In our series diagnosis of type I and type II dissection was significantly more accurate than that of type III dissection. Transoesophageal echocardiography has eliminated some of these difficulties.[33–36] Chest wall configuration, small intercostal space, obesity, pulmonary emphysema, and mechanical respiration limit the diagnositic value of transthoracic echocardiography.

Transoesophageal echocardiography is less pleasant than transthoracic echocardiography; side effects are rare (1%), however. One patient had an attack of asthma and another patient had a transient atrioventricular block. Thus atropine should be ready for rapid injection or should be injected before the procedure in patients with bradycardia. Routine use of atropine seems unnecessary because side effects were not reported in another study of 300 patients.[36] In our patients transoesophageal echocardiography was especially successful for imaging the descending thoracic aorta; it also visualised the aortic root and part of the aortic arch. Interposition of the trachea prevented visualisation of the complete aortic arch. Transoesophageal echocardiography detected dilatation of the aorta and the intimal flap as well as the entry tear of the intimal flap. Furthermore, it also showed movement of the intimal flap. In nine patients we detected spontaneous echocardiographic contrast within the false lumen; this finding has been reported by others.[37,38] This was probably because reduced blood flow had caused aggregation of platelets and erythrocytes.[39]

There was a good correlation between the diameters of all parts of the aorta measured by transoesophageal echocardiography and by computed tomography; though the diameters measured by transoesophageal echocardiography were smaller than those measured by computed tomography. The scanning time required for collection of computed tomographic images (4 s) means that movement of the aorta is included and the aortic diameter is overestimated.

Further studies are needed to evaluate whether non-invasive techniques can replace aortography[36] when, as in two of our patients, complete examination of the thoracic aorta by transthoracic and transoesophageal echocardiography is possible. Angiography could perhaps be limited to the coronary arteries. When transoesophageal echocardiography is not available the descending thoracic aorta can be studied by computed tomography.

Though acute aortic dissection of types I and II require prompt operation,[40–44] there is little or no evidence that patients with chronic asymptomatic dissection need elective operation.[16] There is controversy about whether acute type III dissection should be treated surgically or medically.[16] In chronic type III dissection the indications for surgical intervention are restricted and conservative.[16,43,44] Thus after diagnosis of type III dissection by echocardiography no further diagnostic procedures are necessary in symptom free patients.

In our experience transoesophageal echocardiography complements transthoracic echocardiography, particularly for imaging the distal thoracic aorta. Intimal flaps and dilatation of the aorta caused by a dissection could be demonstrated by this method. Transoesophageal echocardiography seems to be better than computed tomography for demonstrating an intimal flap. Early diagnosis and prompt treatment should improve the prognosis in patients with aortic dissection.[15]

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References

1 Nanda NC, Gramiak R, Shah PH. Diagnosis of aortic root dissection by echocardiography. *Circulation* 1973;**48**:506–13.

2 Krueger SK, Starke H, Forker AD, Eliot RS. Echocardiographic mimics of aortic root dissection. *Chest* 1975;**67**:441–4.

3 Hirschfeld DS, Rodriguez HJ, Schiller NB. Duplication of aortic wall seen by echocardiography. *Br Heart J* 1976;**38**:943–50.

4 Iliceto S, Ettorre G, Francioso G, Antonelli G, Biasco G, Rizzon P. Diagnosis of aneurysm of the thoracic aorta. Comparison between two noninvasive techniques: two-dimensional echocardiography and computed tomography. *Eur Heart J* 1984;**5**:545–55.

5 Schweizer P, Erbel R, Lambertz H, Effert S. Two-dimensional

suprasternal echocardiography in dissection of the thoracic aorta. In: Rijsterburgh H, ed. *Echocardiology*. The Hague: M Nijhoff, 1981:55–60.

6 Kasper W, Meinertz T, Kersting F, Lang K, Just H. Diagnosis of dissecting aortic aneurysm with suprasternal echocardiography. *Am J Cardiol* 1978;**42**:291–4.

7 Mintz GS, Kotler MN, Segal BL, Parry WR. Two dimensional echocardiographic recognition of the descending thoracic aorta. *Am J Cardiol* 1979;**44**:232–8.

8 Bubenheimer P, Schmuziger M, Roskamp H. Ein-und zweidimensionale Echographie bei Aneurysmen und Dissektionen der Aorta. *Herz* 1980;5:226–40.

9 Hanrath P, Kremer P, Langenstein BA, Matsumoto M, Bleifeld W. Transösophageale Echokardiographie. Ein neues Verfahren zur dynamischen Ventrikelfunktionsanalyse. *Dtsch Med Wochenschr* 1981;**156**:523–5.

10 Schlüter M, Kremer P, Hanrath P. Transoesophageal two-dimensional echocardiography in the diagnosis of cor triatriatum in the adult. *J Am Coll Cardiol* 1983;2:1011–5.

11 Schlüter M, Kremer P, Hanrath P. Transesophageal two-dimensional echocardiographic feature of flail mitral leaflet secondary to ruptured chordae tendineae. *Am Heart J* 1984;**108**:609–10.

12 Kremer P, Hanrath P, Langenstein BA, Matsumoto M, Tams C, Bleifeld W. The evaluation of left ventricular function at rest and during exercise by transoesophageal echocardiography in aortic insufficiency [Abstract]. *Am J Cardiol* 1981;**47**:412.

13 Börner N, Erbel R, Braun B, Henkel B, Meyer J, Rumpelt J. Diagnosis of aortic dissection by transoesophageal echocardiography. *Am J Cardiol* 1984;**54**:1157–8.

14 DeBakey ME, Cooley DA, Creech O Jr. Surgical considerations of dissecting aneurysm of the aorta. *Ann Surg* 1955; **142**:586–612.

15 Earnest F, Muhm Jr, Sheedy PF. Roentgenographic findings in thoracic aortic dissection. *Mayo Clin Proc* 1979;**54**:43–50.

16 Doroghazi RM, Slater EE. *Aortic dissection*. New York: McGraw-Hill, 1983:133–64.

17 Harris RD, Usselman JA, Vint VC, Warmath MA. Computerized tomographic diagnosis of aneurysms of the thoracic aorta. *J Comput Assist Tomogr* 1979;**3**:81–91.

18 Sanders JH, Malave S, Niemann HL, Moran JM, Roberts AJ, Michaelis LL. Thoracic aortic imaging without angiography. *Arch Surg* 1979;**114**:1326–9.

19 Suchato C, Pekanan P, Singjaroen T, Sereerat P. Indication of dissecting aortic aneurysm on noncontrast computed tomography. *J Comput Assist Tomogr* 1980;**4**:115–6.

20 Heiberg E, Wolverson M, Sundaram M, Conners J, Susman N. CT findings in thoracic aortic dissection. *Am J Roentgenol* 1981;**136**:13–7.

21 Lardé D, Bellor C, Vasile N, Frija J, Ferrané J. Computed tomography in dissection of the thoracic aorta. *Radiology* 1980;**136**:147–51.

22 Godwin JD, Herfkens RL, Skiöldebrand CG, Federle MP, Lipton MJ. Evaluation of dissection and aneurysms of the thoracic aorta by conventional and dynamic CT scanning. *Radiology* 1980;**136**:125–33.

23 Gross SC, Barr I, Eyler WR, Khaja F, Goldstein S. Computed tomography in dissection of the thoracic aorta. *Radiology* 1980;**136**:135–41.

24 Moncada R, Churchill R, Reynes C, *et al.* Diagnosis of dissecting aortic aneurysm by computed tomography. *Lancet* 1981;**i**:238–41.

25 Egan TJ, Niemann HL, Hermann RJ, Malave SR, Sanders JH. Computed tomography in the diagnosis of aortic aneurysm, dissection or traumatic injury. *Radiology* 1980;**136**:141–6.

26 Moothart RW, Spangler RD, Blount SG. Echocardiography in aortic root dissection and dilatation. *Am J Cardiol* 1975;**36**:11–6.

27 Krueger SK, Wilson CS, Weaver WR, Reese HE, Cavdill CC, Rourke T. Aortic root dissection: echocardiographic demonstration of torn intimal flap. *JCU* 1976;**4**:35–9.

28 Nicholson WJ, Cobbs BW. Echocardiographic oscillating flap in aortic root dissecting aneurysm. *Chest* 1976;**70**:305–7.

29 Victor MF, Mintz GS, Kotler MN, Wilson AR, Segal BL. Two-dimensional echocardiographic diagnosis of aortic dissection. *Am J Cardiol* 1981;**48**:1155–9.

30 Roudant R, Billès MA, Gateau P, Besse P, Dallocchio M. Two-dimensional echocardiography in the diagnosis of aortic dissection in 41 patients [Abstract]. *Circulation* 1981;**64** (suppl IV):314.

31 Nakamura K, Suzuki S, Satomi G, *et al.* Two-dimensional echocardiographic and RI angiographic features of aneurysm of the ascending aorta in patients with annuloaortic ectasia. *J Cardiogr* 1981;**11**:239–52.

32 Bubenheimer P. Fortschritte in der Diagnose der Aortendissektion durch TM-und 2D-Echographie. *Cardiology* 1981;**68** (suppl 1):66–74.

33 Hanrath P, Schlüter M, Langenstein BA, *et al.* Detection of ostium secundum atrial defects by transoesophageal cross-sectional echocardiography. *Br Heart J* 1983;**49**:350–8.

34 Schlüter M, Langerstein BA, Polster J, *et al.* Transoesophageal cross-sectional echocardiography with a phased array transducer system. Technique and initial clinical results. *Br Heart J* 1982;**48:**67–72.

35 Schlüter M, Langenstein BA, Hanrath P, Kremer P, Bleifeld W. Assessment of transesophageal pulsed Doppler echocardiography in the detection of mitral regurgitation. *Circulation* 1982;**66**:787–89.

36 Schlüter M, Hinrich A, Tier W, *et al.* Transoesophageal two-dimensional echocardiography: comparison of ultrasonic and anatomic sections. *Am J Cardiol* 1984;**53**:1173–8.

37 Panidis JP, Kotler MN, Rintz GS, Ross J. Intracavitary echoes in the aortic arch in type III aortic dissection. *Am J Cardiol* 1984;**54**:1159–60.

38 Stern H, Erbel R, Börner N, Schreiner G, Meyer J. Spontaner Echokontrast, registriert mittels transösophagealer Echokardiographie bei Aortendissektion Typ III. *Z Kardiol* 1985;**74**:480–1.

39 Mikell FL, Asinger RW, Elsperger J, Anderson WR, Hodges M. Regional stasis of blood in the dysfunctional left ventricle: echocardiographic detection and differentiation from early thrombosis. *Circulation* 1982;**66**:775–83.

40 Earnest F IV, Muhm JR, Sheedy PF II. Roentgenographic findings in the thoracic aortic dissection. *Mayo Clin Proc* 1979;**54**:43–50.

41 Dalen JE, Alpert JS, Cohn LH, Black H, Collins JJ. Dissection of thoracic aorta. Medical or surgical therapy? *Am J Cardiol* 1974;**34**:803–8.

42 Kirklin JK, Kirklin JW. Invited commentary (to reference 32). *World J Surg* 1980;**4**:578–9.

43 Miller DC, Stinson EB, Shumway NE. Realistic expectations of surgical treatment of aortic dissections: the Stanford experience. *World J Surg* 1980;**4**:571–8.

44 Bergan JJ, Yao JST. *Aneurysms. Diagnosis and treatment*. New York: Grune and Stratton, 1982:105–18.

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Value of combined cross sectional and Doppler echocardiography in the detection of left ventricular pseudoaneurysm after mitral valve replacement

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SUMMARY The development of a left ventricular pseudoaneurysm is a rare complication of heart surgery. Until recently it has been impossible to detect without an angiographic study of the left ventricle. A combination of cross sectional and Doppler ultrasound studies led to the correct diagnosis in two patients with left ventricular pseudoaneurysms after mitral valve replacement. Cross sectional echocardiography showed a posterolateral echo-free space confined only by the pericardium and communicating with the left ventricle through a defect in the ventricular wall, and Doppler echocardiography confirmed the presence of blood flow in this cavity. This Doppler finding is critical if the perforation is too small to be identified reliably by cross sectional imaging. Surgical repair of the pseudoaneurysm can be undertaken without invasive studies if the echocardiographic findings are unequivocal and there is no reason to suspect the integrity of the circumflex coronary artery.

An intraoperative or, more rarely, delayed rupture of the posterior left ventricular wall complicates 0·5% of all mitral valve replacements.[1] About one third of the patients will survive, either because the perforation can be repaired immediately or because firm adhesions limit intrapericardial bleeding.[2] A pseudoaneurysm is formed when adhesions are present or when the defect reopens after initially successful closure. Because perforation is uncommon and the chances of survival are low, cases of left ventricular pseudoaneurysm after mitral valve surgery are rare: a recent study identified only 10 reported cases.[3] This small survey showed that the prognosis is poor in cases of pseudoaneurysm and that surgical repair should be seriously considered as soon as possible after diagnosis.[3–5] Early detection of this complication is important.

Until the last reported case[3] all the diagnoses had been made by angiography or at necropsy. Carlson *et al* first reported on the usefulness of cross sectional echocardiography in this setting.[3] We found that a combination of cross sectional and Doppler echocardiography was a convenient and reliable method of detecting pseudoaneurysms. We believe that under certain circumstances surgical correction of the defect may be undertaken without an antecedent angiographic study.

Patients and methods

PATIENTS

Case 1

We studied two women (aged 66 and 21) with left ventricular pseudoaneurysm after mitral valve replacement. The older patient (case 1) was operated on in March 1986 because of combined mitral valve disease, tricuspid regurgitation, and triple vessel coronary artery disease. In addition to mitral valve replacement with a mechanical prosthesis (Duromedics 27M) she had tricuspid valve annuloplasty and coronary artery bypass surgery. The operation was complicated by a perforation in the posterior left ventricular wall adjacent to the atrioventricular groove. This defect was identified intra-

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operatively and was closed successfully from outside the heart. The patient was discharged on the 36th postoperative day but was readmitted one week later with chest pain, hypotension, and heart failure. She had a murmur suggesting paraprosthetic regurgitation, and a chest radiograph showed a greatly enlarged heart. Combined cross sectional and Doppler echocardiography suggested the presence of a left ventricular pseudoaneurysm and (paravalvar) mitral regurgitation; reoperation was undertaken without any invasive studies. The patient died from pulmonary complications a month after operation.

Case 2

In July 1983 the younger patient (case 2) had acute *Staphylococcus aureus* endocarditis of the mitral valve, which was replaced with a bioprosthesis (Ionescu-Shiley 27M). Operation and the recovery were uneventful although she was allergic to several antibiotics. In February 1984 she had a new episode of staphylococcal septicaemia and an echocardiographic study showed a unusual outward bulge of the posterobasal pericardium during systole. This was difficult to interpret; perforation of the left ventricular posterior wall was one possibility. A cineangiogram of the left ventricle appeared to be normal but was of poor quality. The patient did well and all antibiotic treatment was stopped in March 1985. In May 1986, she was studied as part of a follow up of the results of surgical treatment of infective endocarditis. At clinical examination we found systolic and diastolic murmurs and a systolic parasternal lift.

Echocardiography showed degeneration of the bioprosthesis and an unequivocal left ventricular pseudoaneurysm. Retrospective examination of the left ventricular cineangiogram obtained two years earlier showed faint opacification of the pseudoaneurysm. Reoperation was performed in July 1986, after coronary angiography showed the integrity of the circumflex coronary artery. At operation a subannular pseudoaneurysm (30 mm × 40 mm), thickening of the prosthetic valve cusps, and a separate paraprosthetic ventriculoatrial communication were found. The orifice of the pseudoaneurysm was closed by direct suturing from inside the heart and a new bioprosthesis (Mitroflow 27M) was inserted. The patient made a rapid and uneventful recovery. A Doppler echocardiographic study six weeks after operation suggested recurrence of the pseudoaneurysm. The patient is under close surveillance.

ECHOCARDIOGRAPHIC TECHNIQUE

We used a Toshiba SSH-60A sector scanner and a 3·7 MHz phased array transducer for cross sectional echocardiography. In addition to the standard parasternal and apical approaches, we also used modified apical views to image the posterolateral submitral area. We used a Toshiba SDS-60A Doppler unit incorporated into the SSH-60A sector scanner for the pulsed and continuous wave Doppler examinations. Use of a 2·5 MHz duplex transducer allowed the acquisition of simultaneous or successive images and pulsed Doppler studies as well as successive cross sectional imaging and continuous wave Doppler examinations. We analysed signals in real time by fast Fourier transform and we took hard copies of simultaneous frozen spectral displays and cross sectional images.

Results

CROSS SECTIONAL ECHOCARDIOGRAPHY

In both patients a posterolateral echo-free cavity was seen beside the left ventricle in the apical four chamber and parasternal short axis views of the heart. In case 1 the extracardiac cavity was very large and smoke-like echoes were seen whirling slowly near its periphery. However, no clear cut opening to the left ventricle could be identified on cross sectional imaging (fig 1). In contrast, in case 2 (fig 2) a much smaller cavity communicated with the left ventricle through a wide defect in the posterior ventricular wall. Pronounced systolic pulsation of the pseudoaneurysmal space was seen in case 2.

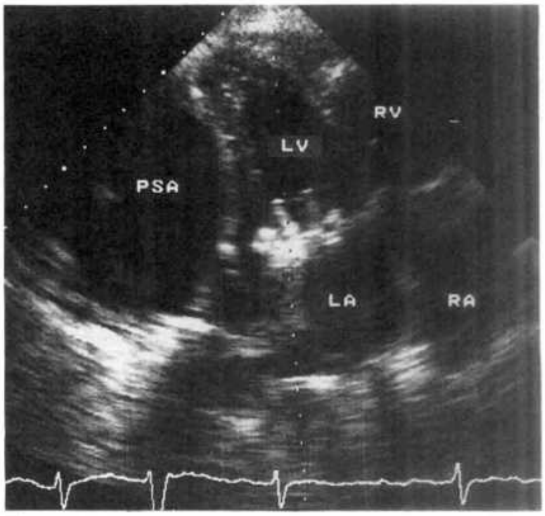


Fig 1 *Apical four chamber cross sectional echocardiogram in case 1 showing a large (70 by 50 mm) extracardiac cavity adjacent to the lateral wall of the left ventricle. Note the two leaflets of the prosthetic valve in open position between the left atrium and left ventricle. LA, left atrium; LV, left ventricle; PSA, pseudoaneurysm; RA, right atrium; RV, right ventricle.*

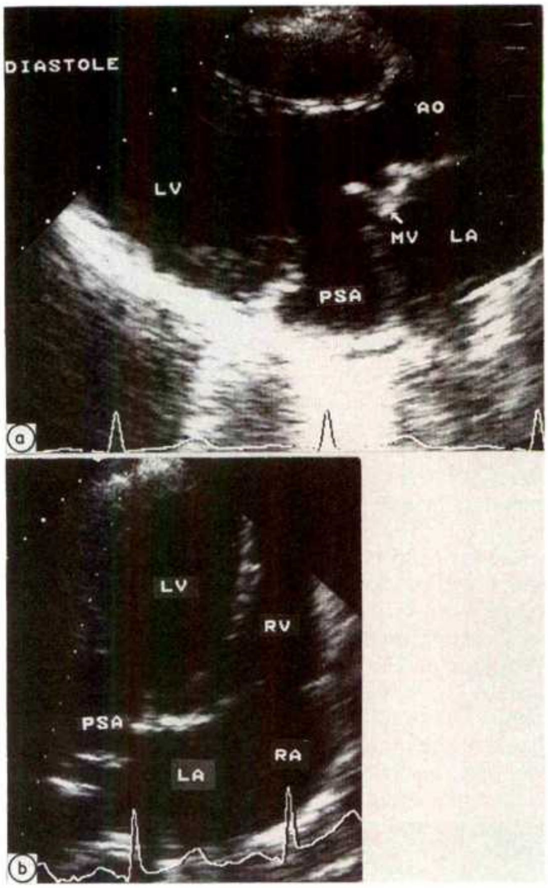


Fig 2 *Parasternal long axis view (a) and the apical four chamber echocardiograms in case 2 (b) showing a posterolateral pseudoaneurysmal cavity just beneath the mitral annulus. AO, aorta; LA, left atrium; LV, left ventricle; MV, mitral valve prosthesis; PSA, pseudoaneurysm; RA, right atrium; RV, right ventricle.*

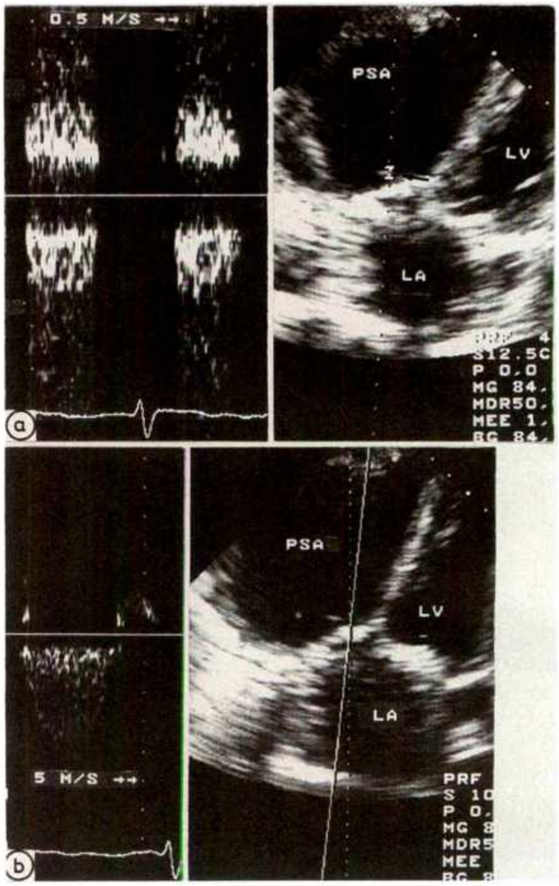


Fig 3 *Pulsed Doppler echocardiography (a) in case 1 showed a strong systolic jet inside the pseudoaneurysm; arrow indicates sampling gate. (b) A continuous wave Doppler study showed a high velocity jet (3·7 m/s) past the prosthesis towards the left atrium; paravalvar regurgitation was confirmed at operation. LA, left atrium; LV, left ventricle; PSA, pseudoaneurysm.*

DOPPLER ECHOCARDIOGRAPHY

Pulsed wave Doppler echocardiography detected unequivocal flow signals inside the extracardiac echo-free space in both patients. In case 1 there was a narrow systolic jet of turbulent high velocity flow near the atrioventricular junction (fig 3a). This jet was discovered when we moved the Doppler gate along the left ventricular wall in the extracardiac space. No audible or recordable flow signals could be detected deeper in the cavity. We found much slower turbulent flow inside the pseudoaneurysmal cavity in case 2 (fig 4).

In case 1 continuous wave Doppler echocardiography uncovered a high velocity systolic jet suggesting paravalvar mitral regurgitation (fig 3b). No signs of paravalvar regurgitation were identified in case 2 but the pressure half time of the transprosthetic flow was slightly prolonged, suggesting degeneration and obstruction of the bioprosthesis.

POST-REPAIR FOLLOW UP

All findings described above were confirmed at operation and later at necropsy in case 1 and at reoperation in case 2. In addition, a paravalvar ventriculoatrial communication, missed on Doppler echocardiography, was found in case 2. In case 1 postoperative Doppler studies were not performed. Case 2 had a follow up examination six weeks after the repair of the pseudoaneurysm. The size of the closed extracardiac cavity by cross sectional echocardiography was the same as before operation

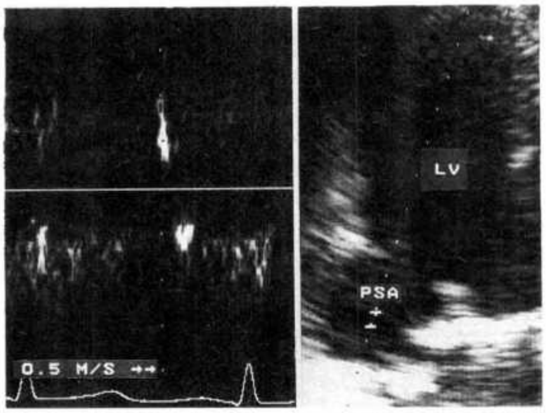


Fig 4 *Pulsed Doppler echocardiography in case 2 combined with an apical cross sectional imaging showed turbulent systodiastolic flow inside the pseudoaneurysm. LV, left ventricle; PSA, pseudoaneurysm.*

(fig 5), but no communication with the left ventricle was visible. Nevertheless, Doppler echocardiography showed unequivocal systodiastolic flow inside the cavity, indicating recurrence of the pseudoaneurysm (fig 5). The flow velocities were clearly higher than before repair. This indicates that the opening between the left ventricle and the pseudoaneurysm was probably smaller than before repair. Cross sectional imaging also suggested a communication between the pseudoaneurysm and the left atrium (fig 5a). The flow signals recorded at the origin of the communication in the pseudoaneurysm were strong; however, they were difficult to detect at its apparent outlet to the left atrium. The presence of a true communication therefore could not be confirmed.

Discussion

Left ventricular pseudoaneurysm after mitral valve replacement usually presents as poor postoperative progress, chest pain, heart failure, peripheral embolisation, and a pansystolic apical murmur. A parasternal systolic lift may also be detected on physical examination,[6] and chest radiography may show an abnormal bulge at the left lateral border of the heart shadow.[5] Though this complex of symptoms and signs can and should alert the clinician to the possibility of a pseudoaneurysm, a definitive diagnosis cannot be made without imaging the left ventricle and neighbouring areas.

Left ventricular cineangiography is the diagnostic procedure of choice.[4 5 7] However, this method is not easy nor does it exclude a false negative diagnosis or misinterpretation. Spellberg and O'Reilly described an error similar to ours (case 2) in the interpretation of left ventricular cineangiography.[4] M mode echocardiography was attempted in several cases but was of little help. The findings were nonspecific, suggesting overload of the left ventricle[5] enlargement of the left atrium and left ventricle,[6] an "abnormal posterior area",[7] or pericardial effusion.[8]

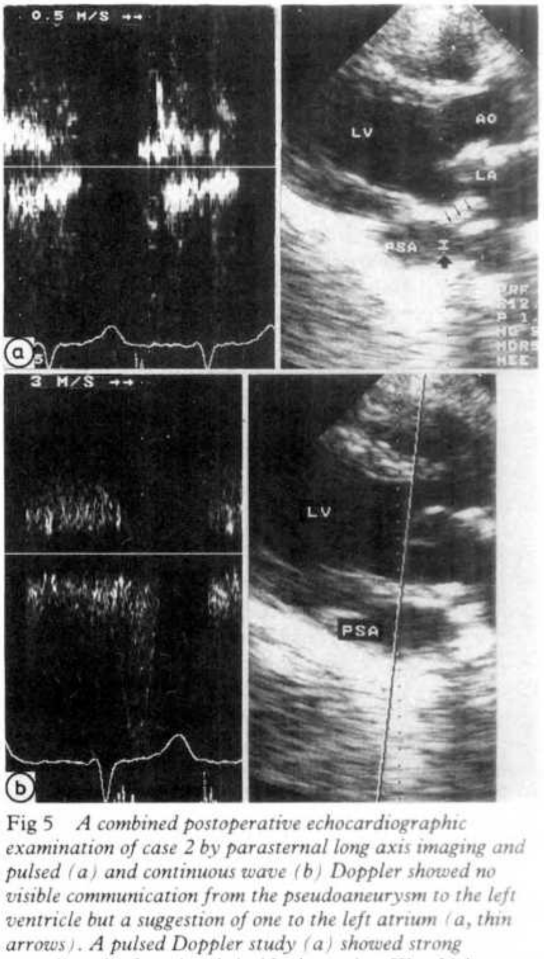


Fig 5 *A combined postoperative echocardiographic examination of case 2 by parasternal long axis imaging and pulsed (a) and continuous wave (b) Doppler showed no visible communication from the pseudoaneurysm to the left ventricle but a suggestion of one to the left atrium (a, thin arrows). A pulsed Doppler study (a) showed strong systodiastolic flow signals inside the cavity. The thick arrow shows the location of the sampling gate. The systolic flow component was of short duration. A continuous wave study (b) showed a high velocity systolic jet (3·5 m/s) of similar timing towards the pseudoaneurysm. These findings suggest a small perforation in the ventricular muscle which closes as the surrounding myocardium contracts. AO, aorta; LA, left atrium; LV, left ventricle; PSA, pseudoaneurysm.*

Recently, Carlson *et al* described the first patient in whom a postoperative submitral pseudoaneurysm was detected by cross sectional echocardiography.[3] Our report supports their experience and also shows the usefulness of a complementary Doppler examination. Together these three cases show on cross sectional echocardiography that a postoperative left ventricular pseudoaneurysm typically presents as a posterolateral echo-free extracardiac cavity. It is best seen in apical views and may escape detection if only a parasternal long axis study is performed. The pseudoaneurysm can measure only two or three centimeters in its longest dimension or can be bigger than the left ventricle. Its orifice, that is the defect in the ventricular wall adjacent to the mitral annulus, can be large and readily detectable or can be so small that it is missed in a cross sectional study. Complementary Doppler study is most important when the defect is small, because by exposing blood flow in the extracardiac space it demonstrates the communication of the defect with the circulation. A careful search of the interface between the echo-free cavity and the left ventricle will detect the flow signals. If the orifice is small and restricted by myocardial contraction a strong flow signal may be identified in its vicinity in the absence of audible or recordable flow deeper in the pseudoaneurysm. Doppler echocardiography can also detect concomitant paravalvar regurgitation but, as our experience indicates, it may be unsuccessful (case 2).

Echocardiography is particularly suitable for follow up of patients after closure of a pseudoaneurysm. The size of the defect can be monitored and the addition of a Doppler examination will indicate whether the repair is intact. A postoperative pseudoaneurysm may be confused with a localised pericardial effusion or a haematoma. The echocardiographic appearance of a pericardial cyst or of the descending aorta are less likely to be misidentified. Apart from the descending aorta, none of these other features show blood flow detectable by Doppler inside their echo-free spaces. A true posterior left ventricular aneurysm can occur after mitral valve replacement if the circumflex coronary artery has been inadvertently ligated near its origin.[9] Cross sectional echocardiography shows that a true aneurysm, unlike a pseudoaneurysm, always has a neck that is wider than its cavity.[10] Others have reported that Doppler echocardiography is useful in the diagnosis of true and false ventricular aneurysms after myocardial infarction.[11 12]

Does the combination of cross sectional and Doppler echocardiography eliminate the need for left ventricular and coronary cineangiography before surgical repair of the pseudoaneurysm? We believe it does, but only if the findings are clear cut and the integrity of the circumflex coronary artery in the atrioventricular groove has been established. The latter requirement is met, for instance, if the proximal circumflex coronary artery has been bypassed at the primary operation, as was the case in our first patient. Otherwise, Doppler echocardiography should not be used in place of angiography but rather as a specific method for detecting postoperative pseudoaneurysms and for monitoring the success of repair operations.

References

1 Achatzy R, Dittrich H, Jelsijevic V, Knoll D, Lunkenheimer PP, Anyanwu E. Rupture of the left ventricle following prosthetic replacement of the mitral valve. *Thorac Cardiovasc Surg* 1979;**27**:48–50.

2 Björk VO, Henze A, Rodriquez L. Left ventricular rupture as a complication of mitral valve replacement: surgical experience with eight cases and review of the literature. *J Thorac Cardiovasc Surg* 1977; **73**:14–22.

3 Carlson EB, Wolfe WG, Kisslo J. Subvalvular left ventricular pseudoaneurysm after mitral valve replacement: two-dimensional echocardiographic findings. *J Am Coll Cardiol* 1985;**6**:1164–6.

4 Spellberg RD, O'Reilly RJ. Pseudoaneurysm of the left ventricle following mitral valve replacement. *Chest* 1972;**62**:115–7.

5 Sharratt GP, Ross JK, Monro JL, Johnson AM. Intraoperative left ventricular perforation with false aneurysm formation. *Br Heart J* 1976;**38**:1154–9.

6 Feint JA, Richardson JP, Clarebrough JD. Subvalvular left ventricular aneurysm following mitral valve replacement. *Aust NZ J Surg* 1975;**45**:151–4.

7 Sutorius DJ, Hormsworth JA, Majevski JA, Miller SF. Repair of a subvalvular left ventricular aneurysm following mitral valve replacement. *Ann Thorac Surg* 1981;**32**:92–6.

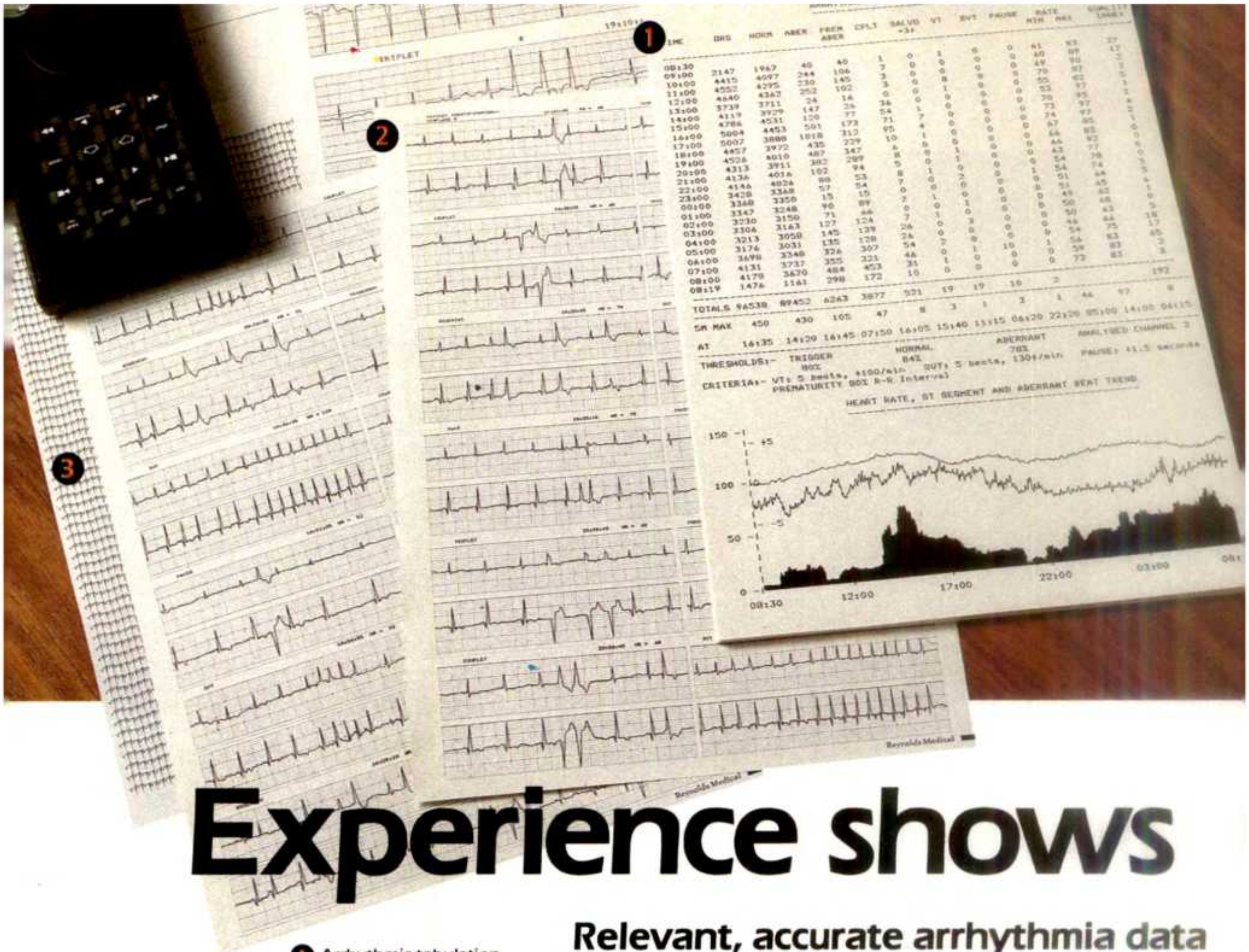
8 Gosalbez F, deLinera FA, Cofino JL, Naya JL, Rodriquez J, Ortuna A. Isolated mitral valve replacement and ventricular rupture: presentation of 6 patients. *Ann Thorac Surg* 1981;**31**:105–10.

9 MacVaugh H, Joyner CR, Johnson J. Unusual complications during mitral valve replacement in the presence of calcification of the annulus. *Ann Thorac Surg* 1971;**11**:336–42.

10 Catherwood E, Mintz GS, Kotler MN, Parry WR, Segal BL. Two-dimensional echocardiographic recognition of left ventricular pseudoaneurysm. *Circulation* 1980;**62**:294–303.

11 Grube E, Redel D, Janson R. Non-invasive diagnosis of a false left ventricular aneurysm by echocardiography and pulsed Doppler echocardiography. *Br Heart J* 1980;**43**:232–6.

12 Loperfido F, Pennestri F, Mazzari M, *et al.* Diagnosis of left ventricular pseudoaneurysm by pulsed Doppler echocardiography. *Am Heart J* 1985;**110**: 1291–3.



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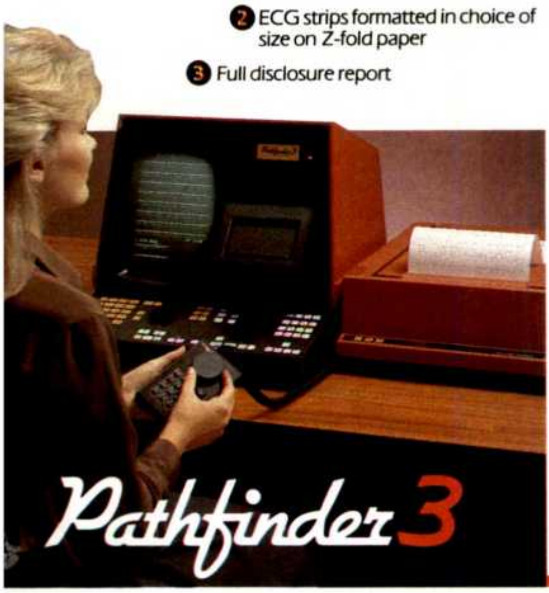

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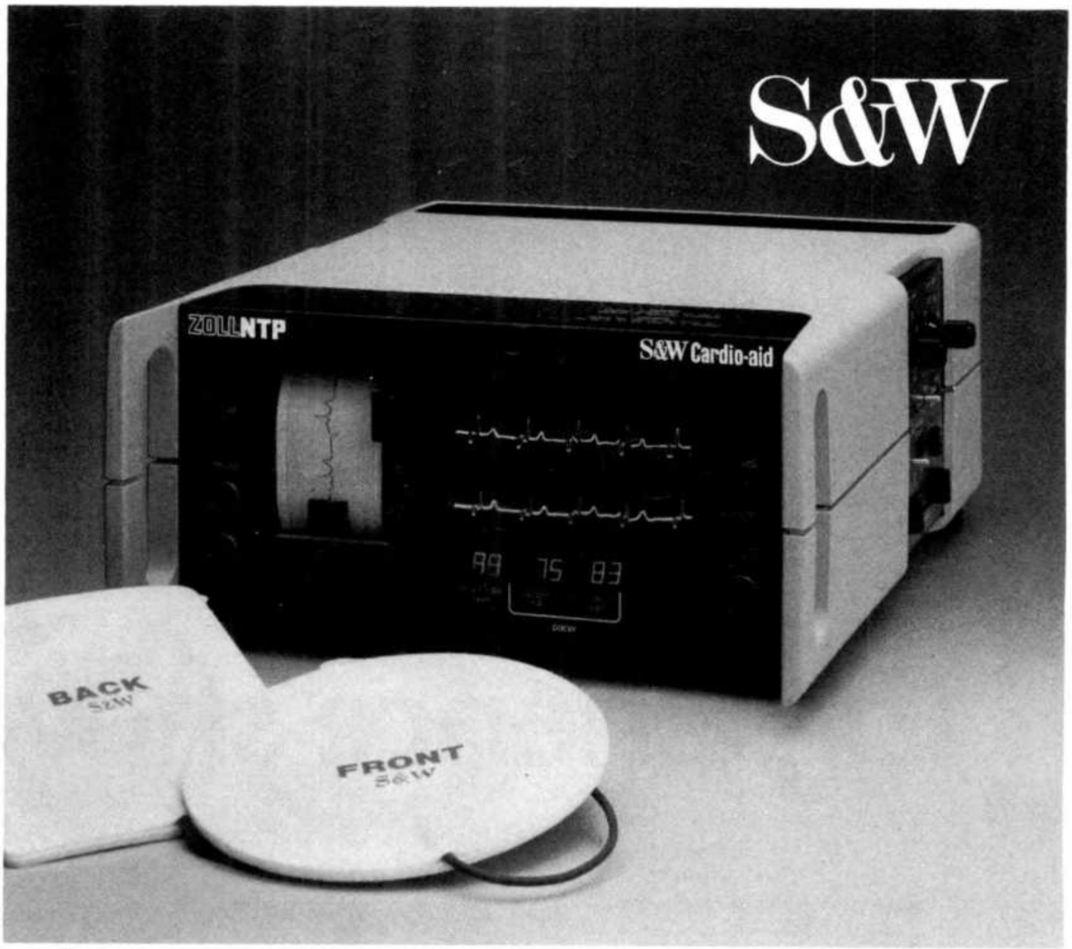

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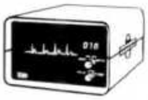
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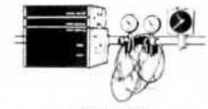
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Infective endocarditis in children with congenital heart disease: comparison of selected features in patients with surgical correction or palliation and those without

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SUMMARY The diagnostic and prognostic features of 44 episodes of infective endocarditis in 42 children with congenital heart disease were reviewed. Endocarditis occurred in 18 patients who had not had surgical correction or palliation of the defect (non-operated group). There were 26 episodes in 24 patients who had been treated surgically (operated group) (16 open and eight closed cardiac operations). Endocarditis occurred soon after open heart surgery in eight patients and as a late complication in the other 16. It recurred in two patients (operated group). Invasive monitoring and low cardiac output were consistent features in those patients who had endocarditis soon after open heart surgery whereas dental treatment was a common feature in non-operated cases and after closed cardiac operations. Late cases of endocarditis after open heart surgery had various microbiological features that were not typical of infection after dental problems. Gram positive infections occurred in non-operated patients and in those who had had closed cardiac operations. The group that had open heart surgery had infections caused by Gram positive, Gram negative, and anaerobic bacteria and fungi. Fever, anaemia, leucocytosis, and positive blood cultures were the only consistent findings. Vegetations were seen in nine of 12 patients at cross sectional echocardiography. All 12 (four non-operated, one closed, and seven open cases) needed acute surgical treatment. The mortality from infective endocarditis was 17% for non-operated cases, 0% for those who had had closed heart surgery, and 50% for those who had had open heart surgery.

Infective endocarditis after open heart surgery differs from that in the other subgroups in terms of microbiology, source of infection, and outcome and its early diagnosis depends on a thorough investigation of minimal symptoms and signs.

Infective endocarditis is an infrequent but serious disease in infants and children. The risk of infective endocarditis is greatest in children with congenital heart lesions, whether or not the defect has been treated surgically. We retrospectively reviewed cases of infective endocarditis treated in the Thoracic Unit of The Hospital for Sick Children, Great Ormond Street, London, between 1965–1983 to determine the clinical and pathological differences between infective endocarditis occurring in the various subgroups studied. This information will be useful in achieving earlier diagnosis and better treatment of infective endocarditis in patients who have surgical correction or palliation of congenital heart lesions. The clinical signs and symptoms of endocarditis in these patients may differ from those normally associated with subacute bacterial endocarditis.

Patients and methods

We reviewed 44 episodes of infective endocarditis in 42 patients. The age at the time of diagnosis of endo-

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carditis ranged from three days to 16 years (mean (SD) 7·8 (4·7) years). Twenty four patients had had operations to correct or palliate their congenital defect and 18 had not. Two of the operated patients had two episodes of infective endocarditis. The episodes were grouped according to the temporal relation between infective endocarditis and previous operation and the type of operation, if any. Early postoperative infective endocarditis was defined as that occurring within 30 days after operation and late infective endocarditis occurred any time after that. Patients with non-operated congenital heart disease were known to have a congenital heart lesion before the episode of infective endocarditis or were diagnosed as having one at the time of presentation. Operations were either complete corrections performed on cardiopulmonary bypass or palliative procedures performed without bypass. For the purposes of this study, patients who had balloon atrial septostomy were included in the group with non-operated congenital heart disease whereas all the patients who had other palliative operations were included in the group that had operation without cardiopulmonary bypass.

The data were analysed by a χ^2, Fisher's exact, or two-tailed Student's *t* test as appropriate, and the relative risks of death from infective endocarditis were calculated for various clinical and pathological features.[1]

Results

Tables 1–6 summarise the data and the various characteristics for each group. The underlying cardiac lesions in these patients produced a spectrum of cyanotic and non-cyanotic problems in all the subgroups (table 1). The interval between operation and infective endocarditis was <30 days in eight patients in the cardiopulmonary bypass group (mean (SD) 6·5 (5·2) days). The remaining cases in the cardiopulmonary bypass and palliative groups occurred much later (mean (SD) 3·2 (3·5) years) and was con-

Table 1 *Diagnosis and previous operations in patients with infective endocarditis*

Patients	*Previous operation*	*No*
Infection early after cardiopulmonary bypass		
Atrioventricular septal defect	Atrioventricular septal defect repair	1
Multiple ventricular septal defects + pulmonary artery banding	Ventricular septal defect closure + debanding	1
Myocardial infarction + fibroelastosis	Mital valve replacement	1
Ventricular septal defect + subaortic stenosis	Ventricular septal defect closure	1
Ventricular septal defect	Ventricular septal defect closure	1
Truncus arteriosus	Truncus arteriosus repair (heterograft and dacron conduit)	1
Transition of the great arteries	Mustard operation (dura mater)	1
Tetralogy of Fallot	Repair of tetralogy of Fallot	2
Infection late after cardiopulmonary bypass:		
Pulmonary atresia + ventricular septal defect	Repair with homograft conduit	1
Pulmonary atresia + ventricular septal defect	Repair with xenograft conduit	1
Transposition of the great arteries + ventricular septal defect + left ventricular outflow tract obstruction	Repair (Mustard + ventricular septal defect closure)	2
Ventricular septal defect + pulmonary artery banding	Ventricular septal defect closure + debanding	1
Atrioventricular septal defect + mitral regurgitation	Repair	1
Ventricular septal defect + aortic insufficiency	Aortic valvuloplasty + ventricular septal defect closure	1
Non-cardiopulmonary bypass:		
Tetralogy of Fallot	Blalock shunt	2
Univentricular heart	Pulmonary artery banding (2), Blalock shunt (1)	3
Double outlet right ventricle + pulmonary stenosis + multiple ventricular septal defects	Blalock shunt	1
Pulmonary atresia + ventricular septal defect	Blalock shunt	1
Tricuspid atresia	Blalock shunt	1
Non-operated		
Ventricular septal defect		9
Patent ductus arteriosus		3
Ventricular septal defect + subaortic membrane		1
Transposition of the great arteries + balloon atrial septostomy		1
Aortic stenosis		1
Subaortic membrane		1
Transposition of the great arteries + left ventricular outflow tract obstruction		1
Transposition of the great arteries + patent ductus arteriosus + balloon atrial septostomy		1
Total		42

sistent with different aetiological factors in these groups. The mean age of operated and non-operated patients was similar ($p < 0·2$). The mean interval between operation and infective endocarditis was similar for the non-cardiopulmonary bypass and cardiopulmonary bypass groups ($p > 0·1$) despite the higher number of early cases in the cardiopulmonary bypass group (table 2). Cases occurring within 30 days of cardiopulmonary bypass were associated with invasive monitoring and low cardiac output; both these features were unusual in non-cardiopulmonary bypass patients.

The source of infection in endocarditis is difficult to prove in any individual case, even if the same organism is cultured from blood and other tissues. Table 3 gives the sources suspected in our cases. In all the early cases after cardiopulmonary bypass there was at least one suspected source for the septicaemia. Most of these were related directly to the surgical procedure and concomitant invasive monitoring. Four of these eight patients had a low cardiac output requiring inotropic support for more than 24 hours after operation, and three had acute renal failure (one requiring peritoneal dialysis). Two of the eight had residual ventricular septal defects after closure. These findings contrasted with those in the other groups of patients. In these groups no source for the septicaemia was identified in 40–60%. For the cardiopulmonary bypass cases only one patient had a suspected dental source for the septicaemia. Dental problems were identified in a significantly ($p < 0·001$) higher proportion of the non-cardiopulmonary bypass (4/8) and non-operated cases (9/18).

Blood cultures were positive in all but three episodes in this study in patients in whom the diagnosis was confirmed at operation or necropsy. Although monomicrobial Gram positive infections were predominant (31 out of 41 episodes) the frequency of Gram negative, fungal, and polymicrobial infections was significantly higher in the cardiopulmonary bypass cases ($p < 0·001$). The most frequently isolated organisms belonged to the streptococcus viridans group (including *Streptococcus mitis* and *Streptococcus sanguis*) (17/41), and *Staphylococcus aureus* (14/41). Fungi were isolated in two cases, occurring coincidentally with viridans infection in the same patient (table 4).

Table 5 summarises the symptoms, signs, and laboratory findings in the patients we reviewed. No individual symptom was present consistently in all groups—the norm was a constellation of non-

Table 2 *Distribution of patients with infective endocarditis and the interval between operation and infection*

	No	*Episodes*	*Mean interval*	*Mean age (yr)*	*Mortality (%)*
Early cases after CPB	8	8	6·6 days	5·0	50
Late cases after CPB	8	10	30·6 mnth	11·3	50
Non-CPB	8	8	48·3 mnth	5·9	0
Non-operated	18	18	—	8·7	17
Total	42	44	—	7·8	26

CPB, cardiopulmonary bypass.

Table 3 *Suspected sources for septicaemia in patients with infective endocarditis*

Suspected source	*Early cases after CPB*	*Late cases after CPB*	*Non-CPB*	*Non-operated*
Central lines	8	—	—	—
Intra-aortic balloon	1	—	—	—
Wound abscess	1	—	—	—
Peritoneal dialysis catheter	2	—	—	—
Tracheostomy wound	1	—	—	—
Necrotising enterocolitis	1	—	—	—
Umbilical artery catheter	1	—	—	—
Tonsillitis	—	1	1	—
Sinusitis	—	1	—	—
Femoral arteriovenous fistula	—	1	—	—
Pneumonia	—	—	1	2
Skin laceration	—	—	—	1
Cardiac catheterisation	—	—	—	1
Dental infection	—	1	2	5
Cutting second tooth	—	—	—	1
Dental instrumentation (with antibiotics)	—	—	2	—
Dental instrumentation (without antibiotics)	—	—	—	3
No source identified	—	6	3	7
Total	15	10	9	20

CPB, cardiopulmonary bypass

specific complaints. Physical examination on the other hand showed fever in nearly every case (39/44) at presentation. A new or changed murmur was found in six out of ten late cases after cardiopulmonary bypass. This was a less frequent finding in early cases after cardiopulmonary bypass, in non-cardiopulmonary bypass cases, and in non-operated cases (3/8, 1/8, 7/18 respectively); and is not significant (p > 0·1). New or increasing congestive heart failure was most common (p < 0·01) in cases presenting soon after cardiopulmonary bypass. Signs traditionally associated with endocarditis were too uncommon to be helpful in early diagnosis. Cross sectional echocardiography was useful in the 12 patients undergoing this examination and showed vegetations in nine.

Complications of the infection itself or of treatment or both were frequent in all groups (mean 0·63–1·9 per episode) (table 6). For the entire group 45 complications occurred in 31 cases (mean 1·18 per episode).

This study did not include a detailed analysis of antibiotic treatment. Patients on our unit received treatment after consultation with microbiologists,

Table 4 *Micro-organisms isolated from blood in patients with infective endocarditis*

Organism	*Early cases after CPB (8)**	*Late cases after CPB (10)**	*Non-CPB (8)**	*Non-operated (18)**	*Total (44)**
Staphylococcus aureus	2	3	—	9	14
Streptococcus viridans group	—	1	3	5	9
Streptococcus mitis + Str sanguis	—	—	—	1	1
Streptococcus viridans group + *Candia albicans*	—	—	1	—	1
Streptococcus pneumoniae	—	—	—	1	1
Corynebacterium	1	—	—	—	1
Escherichia coli	—	—	—	1	1
Pseudomonas aeruginosa	2	—	—	—	2
Klebsiella	1	1	—	—	2
Bacillus fragilis + Proteus vulgaris	—	1	—	—	1
Tinea capitatum	—	1	—	—	1
Candida guillermondi	—	1	—	—	1
None Isolated	2	—	1	—	3

*Total episodes.

Table 5 *Clinical and pathological features of infective endocarditis*

	Early cases after CPB (8)*	*Late cases after CPB (10*)*	*Non-CPB (8*)*	*Non-operated (18*)*
Symptom:				
Vomiting	—	—	—	4
Headache	—	2	1	3
Anorexia	—	2	3	3
Malaise	—	2	3	3
Seizure	—	—	—	1
Weight loss	—	1	—	2
Abdominal pain	—	3	—	1
Rigors	—	—	—	1
Sweating	—	2	2	—
Arthralgia	—	1	1	—
Failure to thrive	—	—	1	1
No symptoms	—	—	1	—
Signs:				
Fever	8	8	7	16
Change in murmur	3	6	1	7
Congestive heart failure (new or increased)	8	3	5	5
Pulmonary embolus	—	3	2	3
Systemic embolus	1	1	—	2
Splenomegaly	—	2	2	3
Cutaneous signs	—	2	2	1
Acute abdomen	—	—	—	1
Lymphadenopathy	—	—	1	—
Laboratory data:				
Anaemia	8	6	5	14
Leucocytosis	8	6	4	12
Abnormal urine sediment	1	1	2	6
Chest *x* ray change	8	3	5	11
Change in electrocardiogram	—	1	—	1

*Total episodes

cardiologists, surgeons, and pharmacists; and in patients who had operation we assumed that appropriate medical treatment had failed. Table 7 summarises the indications for surgical intervention in patients undergoing treatment for infective endocarditis. Late cases after cardiopulmonary bypass were the most likely to require surgery during the initial stage of medical treatment ($p < 0{\cdot}01$). Five patients in the non-cardiopulmonary bypass group and four in the non-operated group had cardiac operations after successful medical treatment for infective endocarditis, not for complications of infective endocarditis per se but rather for the underlying congenital lesions. Overall, 12 of 44 episodes of infective endocarditis had a fatal outcome (27% mortality). The 50% mortality for infective

Table 6 *Complications occurring during treatment of infective endocarditis*

Complication	*Early cases after CPB (8*)*	*Late cases after CPB (10*)*	*Non-CPB (8*)*	*Non-operated (18*)*
Renal failure	2	—	—	—
Septic shock	1	—	—	—
Gastrointestinal bleed	1	—	—	—
Disseminated intravascular coagulation	1	—	—	—
Aortic insufficiency	1	—	—	—
Mitral insufficiency	1	—	—	—
Cerebrovascular accident	1	3	—	2
Aortic aneurysm	1	—	—	—
Pulmonary insufficiency	—	—	—	—
Pulmonary embolus	—	3	1	1
Pulmonary artery aneurysm	—	1	1	—
Superior vena cava obstruction by vegetation	—	—	1	—
Splenic infarction	—	1	1	—
Neutropenia	—	—	—	1
Nephritis (drug)	—	—	—	2
Left ventricular outflow tract obstruction by vegetation	—	1	—	—
Coronary embolus	—	1	—	—
Myocardial abscess	—	1	—	—
Conduit obstruction	—	1	—	—
Homograft valve destruction	—	2	—	—
Death	4	5	—	3
No complications	2	2	4	5

*Total episodes.

Table 7 *Surgical indications during treatment of infective endocarditis (44 episodes, 42 patients)*

Indication	*Operation*	*Patients*
Early cases after CPB.		
Aortic aneurysm (cannulation site)	Resection of aneurysm	
Aortic valve perforation	Aortic valve replacement	1
Aortic dissection, residual ventricular septal defect	Repair of dissection and ventricular septal defect	1
No surgery, patient survived		2
No surgery, patient died		3
Late cases after CPB		
Cerebral emboli	Resection of vegetation	1
Sepsis—continued	Various	4
Pulmonary emboli	Excision of vegetation	1
Pulmonary artery aneurysm	Resection of pulmonary artery aneurysm	1
Conduit obstruction	Conduit replacement	1
No surgery, patient survived		1
No surgery, patient died		1
Non-CPB		
Multiple pulmonary emboli	Excision of vegetations	1
No surgery, patient survived		7
Non-operated		
Aortic insufficiency + vegetation	Aortic valve replacement	1
Pulmonary emboli + tricuspid vegetation	Ventricular septal defect closure, tricuspid valve leaflet excision	1
Aortic insufficiency + vegetation	Aortic valve replacement + residual subaortic membrane	1
Aortic insufficiency + vegetation	Aortic valve plication + excision of vegetation	1
No surgery, patient survived		14

Table 8 *Relative risk of death in infective endocarditis*

Clinical feature	*Factor by which risk of death was increased*
Low cardiac output, congestive heart failure	8·36
Post-cardiopulmonary bypass	4·33
Renal failure	4·2
Non-staphylococcus/streptococcus infection	3·14
Systemic embolus	2·85
Surgery required during treatment	2·70
Conduit infection	1·26

endocarditis after open heart surgery was significantly higher than mortality rates in the other groups ($p < 0·01$). This mortality reflects the summation of the individual risk factors identified in table 8, which are placed in order of adverse effect. These have been analysed in a mathematical format designed to isolate one risk from another.[1] This analysis showed that an individual with infective endocarditis in whom cardiac failure with a low output develops was just over eight times more likely to die from infective endocarditis as a patient without this complication.

Discussion

The large numbers of children surviving palliative or corrective operations for congenital heart disease constitute a population with a new set of risk factors and a more virulent form of infective endocarditis. Thus effective prophylaxis and early diagnosis of infective endocarditis are especially important in this group.

During the 18 year study period the recommended prophylaxis for dental procedures that were likely to produce a bacteraemia was a single large intramuscular dose of penicillin given approximately an hour before the proposed procedure. (Our current policy for oral administration of amoxycillin accords with current adult practice.) This same regimen was used as prophylaxis for cardiac catheterisation until 1975, but since then the procedure has been carried out without antibiotic prophylaxis. Only one case of infective endocarditis was attributed to cardiac catheterisation. During the entire study period there were 500–550 procedures per annum.

Prophylactic measures were used before operation (both on and off bypass) thoughout the study period. They were started one hour before the induction of anaesthesia and were maintained for 7–10 days. The antibiotic regimen used varied considerably throughout the period, and both single and combination policies were used. The choice has been dictated by local microbiological factors, but has always been aimed at providing not only cover against Gram positive and Gram negative bacteria, but also considerable protection against staphylococci. Penicillin and gentamicin plus one of the cephalosporins were used to provide basic cover.

It is difficult to estimate the incidence of infective endocarditis in congenital heart disease because of the wide spectrum of lesions seen. All types of congenital heart lesions are associated with infective endocarditis, with the probable exception of secundum atrial septal defect.[2] In simple ventricular septal defect the risk of infective endocarditis is 1–2·4 per 1000 patient years; associated aortic insufficiency increases the risk.[2–5] After closure of the ventricular septal defect the risk drops but is not completely eliminated.[4 6] The risks of infective endocarditis after aortic valvotomy for aortic stenosis and after cardiac catheterisation have been estimated to be 3·8 and 0·02% respectively.[3 7] In patients with a left ventricle to right atrial shunt (Gerbode type ventricular septal defect) the risk is about 20%.[8] For untreated pulmonary and aortic stenosis the risk of infective endocarditis is 0·2 per 1000 and 1·8 per 1000 patient-years respectively.[4] Although the risk of infective endocarditis is sometimes reduced after intracardiac repair it is likely to be present for life. The risk depends on the lesion. Although our data do not allow calculation of the incidence of infective endocarditis, the number of postoperative cases in the study suggests that it would be a real and continuing problem for paediatric surgical centres. Furthermore, the risk of a second or third episode of infective endocarditis increases geometrically after the initial infection.[9]

The relative rarity of infective endocarditis in patients under two years of age (except for neonates) has been attributed to absence of dental problems in this group.[5] Four of our 18 non-operated patients and two in the early cardiopulmonary bypass group were less than two years old when the infection developed; this suggests that infective endocarditis is not a disease limited to older children. Furthermore, dental factors were rarely identified as aetiological factors in septicaemia leading to infective endocarditis in the post-cardiopulmonary bypass group. Although it has been suggested that infective endocarditis of the right heart is less likely to impair haemodynamic function than the left heart infections, this may apply more to rheumatic valvar disease than to congenital lesions.[10] Infective endocarditis is especially virulent in the presence of a right ventricle to pulmonary artery conduit.

The significantly higher mortality rate for infective endocarditis occurring after cardiopulmonary bypass is likely to be related to the higher frequency that are not Gram positive and to the presence of intracardiac prosthetic material as well as to extracardiac conduits. The risk is enhanced by a low cardiac output. The main reported causes of death in infective endocarditis during the perioperative period have been uncontrollable congestive heart failure caused by valve perforation and uncontrollable sepsis, which was common before antibiotics became available.[11 12]

Death in patients with infective endocarditis may be the result of underlying cardiac problems, of infection, or of side effects of treatment. It may be difficult to judge the relative importance of each. In our series uncontrolled sepsis caused the death of two out of three non-operated patients and aortic insufficiency led to the death of the remaining patient. The deaths associated with sepsis were caused by *Escherichia coli* and a streptococcus. The early deaths after cardiopulmonary bypass were associated with uncontrolled staphylococcal sepsis (two cases) and to a low cardiac output (two cases). Two of the five deaths among the late cases of cardiopulmonary bypass had sepsis (staphylococcal and fungal); two died after cerebral emboli and the fifth after conduit thrombosis. Three of the nine patients who died after cardiopulmonary bypass had right ventricular to pulmonary artery conduits (*vs* 4/42 for the series as a whole). The relative risk of death in those with right ventricle to pulmonary artery conduits was 1·3 and that for infective endocarditis caused by a non-streptococcal/non-staphylococcal organism was 3·14. The relative risk if the patient had congestive heart failure at diagnosis of infective endocarditis was 8·36; this was the highest risk for any feature in the study. Other factors associated with a high risk of death were renal failure and previous cardiopulmonary bypass surgery. The overall mortality of 50% for infective endocarditis after cardiopulmonary bypass surgery for congenital lesions is in the order of that for prosthetic valve endocarditis in adults.[11-16]

Trauma to any epithelial surface especially in the oropharynx and gastrointestinal or genitourinary system can result in bacteraemia. A breach in the endothelium makes the cardiovascular system vulnerable; hence surgical factors such as pacemakers, arterial lines, cardiopulmonary bypass, blood products, and intravenous infusions have all been implicated as the source of infection.[2] If dental extractions ultimately lead to infective endocarditis they usually do so within two weeks in 85% of susceptible patients.[17] A delay between symptoms and diagnosis, an inapparent entry point, and previous antibiotic treatment can all obscure the source. In previous reports, including adult patients with native (that is non-perioperative) infective endocarditis, approximately half had no source identified.[8 18] In the present study only the early cardiopulmonary cases had a (presumptive) source of septicaemia in every patient. A dental source for the septicaemia, for which prophylactic antibiotics might have been given, was suspected in only one of the 18 cardiopulmonary bypass cases. Furthermore, two patients developed infective endocarditis despite prophylaxis with antibiotics before dental procedures. Fully effective antibiotic prophylaxis may be impossible in certain categories of patients (for example those with low cardiac output and renal failure) whether or not they are treated surgically (bypass or non-bypass) because all the potential sources for infection cannot be identified.

Confirmation of suspected infective endocarditis by blood culture was possible in all but three cases of infective endocarditis, and two of these had already been treated with antibiotics.

We found no significant differences in the frequency of positive blood cultures between the groups. This result is different from previously reported series in which the incidence of negative blood cultures was as high as 20%.[19-21] Factors which reduce the blood culture yield include variability in culture techniques, the virulence and growth requirements of the organism, and the site of vegetations. A single dose of antibiotic before admission to hospital can result in negative blood cultures for two weeks.[2] None the less, our high rate of positive cultures may be related to the particular patient population. It is unlikely that true cases of infective endocarditis with negative blood cultures would have been overlooked for the full course of the illness. Right sided infective endocarditis in adult patients has been cited as a potential cause of negative blood cultures,[3] but our data do not support this in childhood.

The predominance of organisms of the streptococcus viridans group and *Straphylococcus aureus* in this study accords with other reports.[22] An increase in the incidence of staphylococcal infective endocarditis has been reported in adults treated by cardiac surgery.[2] In our study staphylococcal infections were most common in the non-operated group. The preponderance of non-Gram positive infections in our cardiopulmonary bypass group is, however, reminiscent of adult patients with prosthetic valve endocarditis, another group known to have a virulent clinical course. Knowledge of the greater likelihood of non-streptococcal and non-staphylococcal infective endocarditis patients who have been on cardiopulmonary bypass may be useful in initiating antibiotic treatment for suspected cases before the results of blood cultures are known.

The relative infrequency of most of the classic clinical findings (other than fever) suggests the importance of intensive investigation of fever when it is the only symptom in patients susceptible to infective endocarditis. The higher frequency of congestive heart failure in cases of endocarditis occurring soon after cardiopulmonary bypass may be partly related to the greater frequency of congestive heart failure in this group even when infective endocarditis is not present. Fever, which was present in nearly all of our patients, has been reported to be absent in 25–30% of blood culture positive patients.[23] This difference may be another characteristic specific to our age group and patient population. Abnormal laboratory results, other than anaemia and leucocytosis, were not sensitive markers for infective endocarditis. These two features are of a low specificity, however. The erythrocyte sedimentation rate and circulating immune complex concentrations were not measured in all patients and these results were therefore not used in this study. These investigations were useful in other series.[2] Operation alone can increase the erythrocyte sedimentation rate.

Echocardiography showed vegetations in nine of 12 patients studied and is now considered to be a standard part of the initial investigation for infective endocarditis.[24 25] Vegetations must be more than 2–3 mm in diameter to be visualised by current echocardiographic techniques. Because vegetations can increase in size repeated examinations are necessary. We now repeat echocardiographic examination every week if this diagnosis is suspected. The weekly study is continued during the early period of antibiotic treatment in confirmed cases, and if the vegetation increases in size antibiotic treatment is reviewed and surgical intervention may be considered.

The frequency of serious and fatal complications of infection and treatment indicate not only the importance of early diagnosis and treatment but also a need for adequate prophylaxis. The frequent requirement for surgical intervention in the late cardiopulmonary bypass group emphasises the virulent course of this type of infective endocarditis. Whereas operation is the only option in many patients (uncontrolled sepsis and recurrent emboli), it can introduce a new set of complications. The morbidity of cardiopulmonary bypass operations in patients with intractable congestive heart failure is high even when active infective endocarditis is not present.

Conclusions

Several points can be made regarding infective endocarditis in the paediatric population. Any patient with a congenital heart lesion, whether untreated, repaired, or palliated, should be considered at risk for infective endocarditis. There appears to be no time limit for the occurrence of infective endocarditis; for many lesions the risk is probably lifelong. Sensitive clinical indicators of infective endocarditis in children are limited to fever, anaemia, and leucocytosis. The presence of any of these features should raise suspicion in susceptible patients. If infective endocarditis is present blood cultures and echocardiography are very likely to confirm the diagnosis and should be done even when probability of infective endocarditis seems low by other criteria. The source of septicaemia is not definable in most cases, especially when the disease develops late after cardiopulmonary bypass. Totally effective antibiotic prophylaxis is therefore impossible. Non-Gram-positive organisms were more common in cases arising after cardiopulmonary bypass and these cases are more likely to need surgical intervention and more likely to die from the combination of the underlying cardiac lesion, infection, and treatment. The complication rate for infective endocarditis is high for all groups and increases when there is a delay in the initiation of treatment. These points serve to re-emphasise the critical importance of early diagnosis, which can be achieved only by thorough investigation of minimal symptoms and signs, especially after cardiopulmonary bypass surgery.

References

1 Armitage P. *Statistical methods in medical research.* Oxford: Blackwell Scientific Publications, 1971.

2 Freedman LR. *Infective endocarditis and other intravascular infections.* New York: Plenum, 1982.

3 Keith JD, Rowe RD, Vlad P. *Heart disease in infancy and childhood.* New York: Macmillan, 1978.

4 Gersony WM, Haynes CJ. Bacterial endocarditis in patients with pulmonic stenosis, aortic stenosis or ventricular septal defect *Circulation* 1977;56:84–6.

5 Corone P, Doyon F, Gadeau S, *et al.* Natural history of ventricular septal defect. A study involving 790 cases. *Circulation* 1977;55:908–15.

6 Shaw P, Singh WSA, Rose V, Keith JD. Incidence of bacterial endocarditis in ventricular septal defects. *Circulation* 1966;34:127–31.

7 Braunwald E, Swand HJC. *Cooperative study on cardiac catheterisation (Monograph 20).* New York: The American Heart Association, 1968

8 Deverall PB, Taylor JFN, Aberdeen E, Waterston DJ. Left ventricular right atrial communication. *Ann Thorac Surg* 1969;8:498–505.

9 Sipes JN, Thompson RL, Hook EW. Prophylaxis of infective endocarditis: a re-evaluation. *Annu Rev Med* 1977;28:371–91.

10 Arbulu A, Asfaw I. Infective endocarditis. In: Glenn WWL, ed. *Thoracic and cardiovascular surgery.* Norwalk: Appleton Century Crofts, 1983.

11 Cohen L, Freedman LR. Damage to the aortic valve as

a cause of death in bacterial endocarditis. *Ann Intern Med* 1961,55:562–4.

12 Kaye D. Cure rates and long term prognosis. In: Kaye D, ed. *Infective endocarditis.* Baltimore: University Park Press, 1976:201–11.

13 Kay JH, Bernstein S, Tsuji HK, *et al.* Surgical treatment of candida endocarditis. *JAMA* 1968; 203:621–6.

14 Jamieson MPG, Rees PG, Stark J, de Leval M. Tricuspid endocarditis with ventricular septal defect. *Thorac Cardiovasc Surg* 1980;**28**:48–50.

15 Richardson JV, Karp RB, Kirklin JW, Dismules WE Treatment of infective endocarditis: a 10 year comparative analysis *Circulation* 1978,58:589–97.

16 Watanakunakorn L. Prosthetic valve endocarditis. *Prog Cardiovasc Dis* 1978;22:181–92.

17 Starkebaum M, Durack D, Beeson PB. The "incubation period" of subacute bacterial endocarditis. *Yale J Biol Med* 1977;50:49–58.

18 Pelletier LL, Petesdorf RG. Infective endocarditis. a review of 125 cases from the University of Washington Hospitals: 1963–1972. *Medicine (Baltimore)* 1977;**46**(4):287–313.

19 Pesanti EL, Smith IM. Infective endocarditis with negative blood cultures—an analysis of 52 cases. *Am J Med* 1979;**66**:43–50.

20 Editorial. Infective endocarditis with negative blood cultures. *Br Med J* 1979;**ii**:4.

21 Cannady PB, Sanford JP. Negative blood cultures in infective endocarditis: a review. *South Med J* 1976;**69**:1420–4.

22 Johnson DH, Rosenthal A, Nadas AS. A 40 year review of bacterial endocarditis in infancy and childhood. *Circulation* 1975;**51**:581–8.

23 Teich EM. Afebrile bacterial endocarditis. *J Mount Sinai Hosp* 1968;**35**:566–77.

24 Rubenson DS, Tucker CR, Stinson EB, *et al.* The use of echocardiography in diagnosing culture negative endocarditis. *Circulation* 1981;**64**:641–6.

25 Stram J, Becker R, Davis R. Echocardiographic and surgical correlations in bacterial endocarditis. *Circulation* 1980;**62**(1):164–7.

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Fifty cases of late prosthetic valve endocarditis: improvement in prognosis over a 15 year period

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SUMMARY The clinical course, prognostic factors, and management of 50 cases of late prosthetic valve endocarditis, occurring more than two months after valve replacement, were reviewed. Twenty nine cases that presented from 1971 to 1980 were compared with 21 cases that presented from 1981 to 1985. Apart from an appreciable decrease in the frequency of neurological complications between the first period (38%) and the second period (10%) no differences in clinical or bacteriological features were seen. Seventeen (59%) of the 29 cases in the earlier period and four (19%) of the 21 cases in the later period died. The rationale for antimicrobial treatment was similar during both periods. Cardiac surgery was performed in eight of 29 cases between 1971 and 1980 and in 11 of 21 between 1981 and 1985; the mean (SD) time between diagnosis of endocarditis and operation was 28 (19) days and 43 (44) days respectively. Six of the eight cases operated on in the first period died as did two of the 11 operated on in the second period. Twenty seven of the 29 cases presenting between 1971 and 1980 were treated with anticoagulants—either warfarin (15 of 27) or heparin sodium (12 of 27). Sixteen of the 21 cases presenting later were given anticoagulants and 15 of these cases were given heparin sodium. Control of anticoagulation was inadequate in nine of the 27 cases treated with anticoagulants during the first period and in only two of 16 treated during the second period. During the first treatment period neurological complications were more frequent when control of anticoagulation was inadequate.

Since the first reports of prosthetic valve endocarditis in 1962–63[1] the number of cases has increased. This is the result of an increase in the number of patients undergoing valve replacement and of the longer survival of these patients. The overall prevalence of late prosthetic valve endocarditis, however, remains approximately 1·2%.[2]

In a review in 1979 of 140 cases of late prosthetic valve endocarditis Watanakunakorn reported a mean death rate of 45%.[3] The wide variation in mortality (from 18% to 67%) in various series indicates that many factors can influence prognosis.[4 5]

We have already reported our experience with 29 cases of late prosthetic valve endocarditis studied retrospectively from 1971 to 1980 at the Claude Bernard Hospital.[6] We have reviewed a further 21 cases examined between 1981 and 1985 and we have compared them with the earlier series in an attempt to analyse the factors contributing to any changes in the pattern and prognosis of the disease.

Patients and methods

From January 1971 to December 1985 there were 50 cases of late prosthetic valve endocarditis among the 449 cases of infective endocarditis seen at the Department of Infectious and Tropical Diseases, Claude Bernard Hospital, Paris.

Late prosthetic valve endocarditis was defined as an infection occurring more than two months after valve replacement.[7] Diagnosis was based on the following criteria: *(a)* anatomical evidence of endocarditis (22/50 cases) and *(b)* at least two positive blood cultures containing the same organism and a consistent clinical picture (43 of 50 cases). In the seven cases with negative blood cultures the diagnosis was confirmed anatomically in five and was prob-

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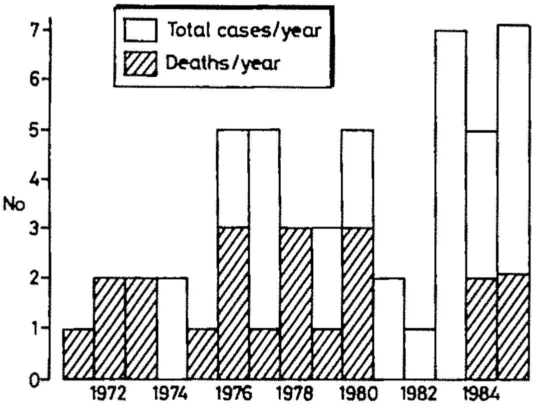

Figure *Number of cases and mortality of late prosthetic valve endocarditis, 1971–85.*

able in two. A relapse was defined as a subsequent episode of endocarditis in which the same organism as in the original episode was implicated and a recurrence as a subsequent episode in which an organism other than the original one was implicated.

The cases were divided into two groups (figure). Twenty nine cases occurred during the earlier period (between 1971 and 1980) in 26 patients (17 men and nine women; mean (SD) age 51 (14) years (range 20–70)). One patient had three recurrences. There were twenty one further cases during the later period (between 1981 and 1985) in 20 patients (13 men and seven women; mean (SD) age 46 (19) years, range 11–75) and one patient had a recurrence.

The two periods were compared by the χ^2 test (both with and without Yates' correction), the Fisher exact probability test, the Mann-Whitney U test, the analysis of variance, and Student's *t* test. A p value of $\leqslant 0{\cdot}05$ was taken to indicate statistical significance.

Results

CLINICAL AND BACTERIOLOGICAL FEATURES

During the first period all 29 cases had mechanical valves, whereas during the second period eight of 21 had heterograft valves ($p < 0{\cdot}001$). The sites of the prostheses were similar in the two periods (table 1).

The only significant difference in the clinical features of the disease between the two periods was the decrease in cerebral events, from 11 (38%) of 29 cases in 1971–80 to two (10%) of 21 cases in 1981–85 ($p < 0{\cdot}05$) (table 2).

There was no significant difference in the bacteriological profile between the two groups (table 3). The frequency of non-streptococcal endocarditis (16/29 in 1971–80 and 11/21 in 1981–85) was similar during the two periods.

Table 1 *Comparison of the site of the prostheses in late prosthetic valve endocarditis between two groups treated over two periods*

	Number of cases	
	1971–80	*1981–85*
Aortic	9	12
Mitral	8	3
Tricuspid	0	3
Multiple	12	3
Total	29	21

Table 2 *Clinical features in cases of late prosthetic valve endocarditis during the two periods*

	Number of cases (%)	
	1971–80 (29 cases)	*1981–85 (21 cases)*
Fever	29 (100)	20 (95)
Splenomegaly	7 (24)	5 (24)
New heart murmur	13 (45)	11 (52)
Congestive heart failure	17 (59)	10 (48)
Cerebral event	11* (38)	2* (10)

*The only significant difference between the two periods was that for cerebral events ($p < 0{\cdot}05$).

Table 3 *Bacteriological features of cases of late prosthetic valve endocarditis during the two periods*

	Number of cases (%)	
	1971–80	*1981–85*
Streptococcus ·	13* (45)	10* (48)
Str enterococcus (group D)	7	4
Str bovis (group D)	3	1
Non-group D	3	5
Staphylococcus ·	10 (34)	3 (14)
Staph aureus	6	2
Coagulase negative	4	0
micrococcus sp	0	1
Other micro-organism	2†	3‡
Two causative agents	3§	1¶
Negative blood and valve cultures	1	4**
Total	29	21

*Frequency of streptococcal endocarditis in the two periods (p = NS).

†*Klebsiella* in one case and *Pseudomonas* in the other.

‡*Corynebacterium* in one case, *Cardiobacterium hominis* in one, and *Histoplasma capsulatum* in one case

§*Streptococcus faecalis* and *Pseudomonas stutzeri* in one case, *Staphylococcus* coagulase negative and *Candida tropicalis* in one case, and *Streptococcus faecalis* and *Enterobacter cloacae* in one case.

¶*Streptococcus sanguis* 1 and *Streptococcus sanguis* 2 in one case.

**Serological evidence of *Coxiella burnetii* endocarditis in one case.

OUTCOME

The overall mortality for the two periods was 42% (21 of 50 cases). Seventeen (59%) cases in the first group died and four (19%) in the second ($p < 0{\cdot}01$). Death was related to cardiac failure in 10 of the 17 earlier cases and in two of the four later cases; a neurological complication accounted for the deaths of seven of 17 cases from 1971 to 1980 and two of the four cases from 1981 to 1985.

The only relapse occurred in the more recent period in a patient who was treated with antimicrobials alone for endocarditis caused by *Streptococcus D faecium*. This patient was successfully treated with antimicrobials and valve replacement. Between 1971 and 1980 one patient died after three recurrences caused by *Streptococcus faecalis,* and finally *Streptococcus bovis* and *Pseudomonas aeruginosa*. Between 1981 and 1985 there was one recurrence caused by *Straphylococcus aureus* in a drug addict with a tricuspid prosthesis who had previously been infected with *Streptococcus sanguis*.

ANTIMICROBIAL TREATMENT

All but one of the 50 cases was treated with antibiotics; in the first period one patient died before treatment could be started. The choice of antimicrobial agents was based on the same principles during both periods; the agent was selected according to the causative organism, the in vitro susceptibility tests, and the serum bactericidal titre. A combined drug regimen was used in 45 of 47 cases of non-fungal endocarditis. The mean (SD) interval between the first manifestations of endocarditis and the onset of antimicrobial treatment was 23 (18) days (range 2–59) for 1971–80 and 25 (36) days (range 2–145) for 1981–85 (NS). The duration of treatment in non-fungal endocarditis was significantly longer in recent years—54 (32) days (range 3–146) versus 34 (20) days (range 2–80) ($p < 0\cdot01$). In 1971–80, however, seven of 27 patients died before day 15 of treatment, whereas in 1981–85 only one of 20 patients did.

SURGICAL TREATMENT

Nineteen patients underwent valve replacement during the active phase of the disease (eight of the 29 initial cases and 11 of the 21 more recent cases). Analysis of prognostic factors from 1971 to 1980[6] led to more precise indications for operation being applied in recent years; these were based on criteria established by Karchmer *et al.*[8] Thus operation was more common during 1981–85; however, this difference was not statistically significant ($p = 0\cdot08$). The mean (SD) interval between the diagnosis of endocarditis and the valve replacement was not significantly different during the two periods: 28 (19) days (range 2–60) in 1971–80 and 43 (44) days (range 8–150) in 1981–85. In the first period, six (75%) of eight surgically treated patients died and in the second period two (18%) of 11 died ($p < 0\cdot05$). Culture of the prosthesis in 17 of 19 surgically treated cases was sterile in eight cases. In seven others it grew the same or one of the organism(s) present in the blood cultures and in two cases it grew an organism which had not been isolated from the blood—*Histoplasma capsulatum* in one case and *Streptococcus mitis* in the other.

ANTICOAGULANT TREATMENT

Anticoagulant treatment was continued in 43 of 50 cases in which it had been used before the development of endocarditis. From 1971 to 1980, 27 of 29 cases were given anticoagulants—15 warfarin and 12 heparin sodium. During this period two patients treated with warfarin had neuromeningeal bleeding with a prothrombin time of less than 10%, without the dose of anticoagulant being changed. For this reason during the second period we treated 15 of 16 cases with heparin sodium rather than warfarin. Satisfactory coagulation tests (that is, activated partial thromboplastin time between 1·5 and 2·5 times control or prothrombin time between 20% and 40% control) were more often maintained during recent years, 14 of 16 cases, than in the past, 18 of 27 cases.

During the first period, neurological complications were more frequent when anticoagulation was inadequate ($p < 0\cdot05$) (table 4). Between 1971 and 1985 two of the seven patients who were not treated with anticoagulants had a cerebral embolus and one had cerebral bleeding related to severe thrombopenia. Neurological signs were an early manifestation of endocarditis occurring before the start of treatment, in six of 11 cases between 1971 and 1980 and in the two recent cases with cerebral events.

PROGNOSTIC FACTORS

There was no significant difference in mortality (expressed as a percentage of cases) between men (12 of 30 (40%)) and women (nine of 16 (56%)), or between cases with mitral endocarditis (five of 11 (45%)), aortic endocarditis (eight of 21 (38%)), tri-

Table 4 *Correlation between neurological complications and anticoagulant treatment in cases of late prosthetic valve endocarditis occurring during two periods*

	Number of cases with cerebral events as a proportion of cases	
	1971–80	*1981–85*
Anticoagulants given	9/27	1/16
Adequate anticoagulation	3†/18*	1†/14
Inadequate anticoagulation	6‡/9*	0/2
Anticoagulants not given	2/2	1/5
Total	11/29	2/21

*$p < 0\cdot05$.

†Probable embolus in two cases and probable haemorrhage in two cases

‡Probable embolus in three cases and probable haemorrhage in three cases.

cuspid endocarditis (one of three (33%)), or multiple valve endocarditis (seven of 15 (47%)). The age of these who died and those who survived was similar. When heterograft valves were affected the death rate was 25% (two of eight cases). This was not significantly different from the death rate in endocarditis of mechanical valves (19 of 42 cases (45%)). The results of cross sectional echocardiography combined with pulsed Doppler could only be studied from 1981 to 1985. This technique provided evidence for the diagnosis of endocarditis—that is, vegetations (seven cases) or valve dysfunction (six cases) in 11 of the 19 cases studied. Two of the seven cases with vegetations died. Six of them had had valve replacement.

Several factors were associated with a less favourable outcome (tables 5 and 6). The predictive value (that is the number of deaths compared with the number of cases with the risk factor) of atrioventricular conduction abnormality, fever persisting for over 10 days despite adequate antibiotic treatment, and neurological complication was similar during both periods. Cardiac failure caused by valve dysfunction was indicative of poor prognosis in the first period only. An isolated new regurgitant murmur was not associated with a poor prognosis—two patients of the eight cases died. Neither was operated upon. The prognosis of cases of non-streptococcal endocarditis (14 deaths out of 16 cases) was significantly worse than the prognosis of cases of streptococcal endocarditis (three deaths out of 13 cases) between 1971 and 1980 ($p < 0{\cdot}001$). However, from 1981 to 1985 the outcome of these two groups was not different; there were three deaths out of 11 cases of non-streptococcal endocarditis and one death out of 10 cases of streptococcal endocarditis.

Table 5 *Comparison of factors in the prognosis in late prosthetic valve endocarditis between two periods. Figures are numbers of deaths/numbers of cases*

	1971–80	*1981–85*	*Significance*
Cardiac failure with new regurgitant murmur	8/9	1/7	$p = 0{\cdot}01$
Conduction abnormality	3/3	—	
Neurological event	10/11	2/2	NS
Persistent fever	6/9	3/11	NS
Streptococcal infection	3/13	1/10	NS
Non-streptococcal infection	14/16	3/11	$p < 0{\cdot}05$
Total	17/29	4/21	$p < 0{\cdot}01$

NS, not significant.

Table 6 *Comparison of the mortality in late prosthetic valve endocarditis between two periods, according to the treatment. Figures are numbers of deaths/number of cases (%)*

	1971–80	*1981–85*	*p value*
Antimicrobial agents alone	11/21 (52)	2/10 (20)	NS
Antimicrobial agents + operation	6/8 (75)	2/11 (18)	$<0{\cdot}05$
Total	17/29 (59)	4/21 (19)	$<0{\cdot}01$

NS, not significant.

Table 7 *Comparison of the mortality in late prosthetic valve endocarditis between two groups treated during two periods, according to the type of micro-organism and the treatment. Figures are numbers of deaths/number of cases*

	Antimicrobials alone	*Antimicrobials and operation*
Streptococcal endocarditis.		
1971–80	3/11	0/2
1981–85	0/5	1/5
Non-streptococcal endocarditis:		
1971–80	8/10	6/6*
1981–85	2/5	1/6*

*$p = 0{\cdot}015$.

The mortality associated with the type of organism and treatment during the two periods could not be compared because the numbers of cases were too small. The prognosis of surgically treated cases of non-streptococcal endocarditis seems to be better in the second period, however (table 7).

Discussion

This study indicates a considerable improvement in the prognosis of late prosthetic valve endocarditis between 1971–80 and 1981–85. The overall mortality was similar to that seen in a review of published series in 1982 in which the case-fatality rate for 193 cases was 46%.[2] Many factors may have contributed to this trend; some are related to the general improvement in medical care and surgical procedures and are thus difficult to analyse. Thus the differences between two successive periods must be interpreted with care. But an improvement in the treatment of late prosthetic valve endocarditis has been noted by others too.[4 9 10]

A comparison of clinical features in our study showed that the pattern of the disease has not changed significantly, except for a decrease in the frequency of neurological events in recent years. Neurological complications are one of the most important causes of death in prosthetic valve endocarditis[6 11] and they are usually associated with a high death rate.[8] A reduction in their occurrence may have been a major factor accounting for the improvement in prognosis between 1981 and 1985. This trend may be related to a change in the management of anticoagulants in recent years. The use of anticoagulants in late prosthetic valve endocarditis has been controversial.[8 11–14] Wilson *et al* emphasised that they should be temporarily discontinued only if a neurological event occurred.[15] In our series anticoagulant treatment was continued in all patients to whom they had been given before the development of endocarditis. The position of patients who are not on anticoagulants when endocarditis is diagnosed is still being debated.[11,12] The numbers of such patients have increased with the use of heterograft valves, which do not require long term anticoagulation.

Our study confirms that anticoagulation must be maintained in a narrow therapeutic range to decrease the frequency and the severity of neurological complications.[16,17] We believe that intravenous heparin sodium is the best anticoagulant for patients with prosthetic valves. Stable anticoagulation cannot be achieved with warfarin, which may be affected by other drugs and infection.[18] The increased use of heparin sodium in our patients probably contributed to the decrease in neurological complications and thus to the improvement in prognosis during recent years. The only two neurological events that occurred between 1981 and 1985 were the first manifestation of endocarditis in both cases. We believe that heparin sodium should be used routinely when anticoagulants are indicated and as soon as the diagnosis of late prosthetic valve endocarditis is suspected.

Bacteriological factors may also have influenced the changing prognosis of late prosthetic valve endocarditis. Like others we found that streptococcal endocarditis was associated with a better outcome than other infections.[2,15] In our study the predominance of streptococci and the less common occurrence of staphylococci (especially *Staphylococcus aureus*) may have reduced mortality in 1981–85; however, the prognosis of streptococcal endocarditis was not different in the two periods, whereas there was a pronounced improvement in the outcome of non-streptococcal endocarditis in recent years.

Advances in treatment in the past few years have improved the prognosis of patients with prosthetic valve endocarditis.[19] The effect of better medical management is difficult to assess. The principles of antimicrobial treatment remained the same—that is, a combined drug regimen of bactericidal agents with bacteriological tests[2,15]—however, more potent antibiotics may have improved the prognosis of patients with non-streptococcal endocarditis.[20]

Differences in surgical treatment between the two periods are more obvious. An analysis of prognostic factors from 1971 to 1980[6] led us to formulate more precise indications for operation in recent years; these were based on the same criteria as those established by Karchmer *et al.*[8] The significant decrease in mortality of surgically treated cases between the two periods is probably another important factor in the improved prognosis in our series. Similar findings were reported by Mayer and Schoenbaum[2] when they reviewed five series.[7,16,21–23] We found that improved surgical management[24–26] was of particular benefit in those with non-streptococcal endocarditis (table 7).

Our study confirmed the validity of most of the criteria for operation established by Karchmer *et al*[8] and reviewed by others.[15,27] Unlike others we did not find that aortic and mechanical valves were associated with a worse prognosis.[5,9,27] The presence of heterograft valves in the patients seen between 1981 and 1985, however, may have been instrumental in reducing the death rate. Cardiac failure due to valve dysfunction did not cause a higher death rate in recent years; all seven cases were treated by surgery. Embolic manifestations, infection with a fungal agent, and relapse have also been proposed as indications for operation,[8,15,27] but these cannot be evaluated in our study. The prognostic value of echocardiographic abnormalities must be confirmed by more extensive studies. Multiple factorial analysis of a greater number of cases may provide more precise indications for operation. Operation is an important factor in the improvement of prognosis of late non-streptococcal prosthetic valve endocarditis.

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References

1 Geraci JE, Dale AJD, McGoon DC. Bacterial endocarditis and endarteritis following cardiac operations. *Wis Med J* 1963;62:302–15.

2 Mayer KH, Schoenbaum SC. Evaluation and management of prosthetic valve endocarditis. *Prog Cardiovasc Dis* 1982;25:43–54.

3 Watanakunakorn C. Prosthetic valve infective endocarditis. *Prog Cardiovasc Dis* 1979;22:181–92.

4 Richardson JV, Karp RB, Kirklin JW, Dismukes WE. Treatment of infective endocarditis. A 10 years comparative analysis. *Circulation* 1978;58:589–97.

5 Masur H, Johnson WD. Prosthetic valve endocarditis. *J Thorac Cardiovasc Surg* 1980;80:31–7.

6 Leport C, Vilde JL, Bricaire F, *et al.* Late prosthetic valve endocarditis: bacteriological findings and prognosis in 29 cases. *Eur Heart J* 1984;5:139–43.

7 Dismukes WE, Karchmer AW, Buckley MJ, Austen WG, Swartz MN. Prosthetic valve endocarditis. Analysis of 38 cases. *Circulation* 1973;48:365–77.

8 Karchmer AW, Dismukes WE, Buckley MJ, Austen WG. Late prosthetic valve endocarditis. Clinical features influencing therapy. *Am J Med* 1978;64: 199–202.

9 Rossiter SG, Stinson EB, Oyer PE, *et al.* Prosthetic valve endocarditis. Comparison of heterograft tissue valves and mechanical valves. *J Thorac Cardiovasc Surg* 1978;76:795–802.

10 Westaby S, Oakley C, Sapsford RN, Bentall HH. Sur-

gical treatment of infective endocarditis with special reference to prosthetic valve endocarditis. *Br Med J* 1983;**287**:320–3.

11 Carpenter JL, McAllister CK, and the US Army Collaborative Group. Anticoagulation in prosthetic valve endocarditis. *South Med J* 1983;**76**:1372–5.

12 Horstkotte D, Korfer R, Loogen F, Rosin H, Bircks W. Prosthetic valve endocarditis. Clinical findings and management. *Eur Heart J* 1984;**5**:117–22.

13 Wilson WR, Geraci JE, Danielson GK, *et al.* Anticoagulant therapy and central nervous system complications in patients with prosthetic valve endocarditis. *Circulation* 1978;**57**:1004–7.

14 Johnson WD. Prosthetic valve endocarditis. In: Kaye D, ed. *Infective endocarditis*. Baltimore: University Park Press, 1976:129–42.

15 Wilson WR, Danielson GK, Giuliani ER, Geraci JE. Prosthetic valve endocarditis. *Mayo Clin Proc* 1982;**57**:155–61.

16 Garvey GJ, Neu HC. Infective endocarditis: an evolving disease. *Medicine (Baltimore)* 1978;**57**:105–26.

17 Pruit IT, Rubin RH, Karchmer AW. Neurological complications of bacterial endocarditis. *Medicine (Baltimore)* 1978;**57**:329–43.

18 Qureshi GD, Reinders TP, Somori GJ, Evans HJ. Warfarin resistance with nafcillin therapy. *Ann Intern Med* 1984;**100**:527–9.

19 Ivert TSA, Dismukes WE, Cobbs CG, *et al.* Prosthetic valve endocarditis. *Circulation* 1984;**69**:223–32.

20 Karchmer AW, Archer GL, Dismukes WE. Rifampin treatment of prosthetic valve endocarditis due to *Staphylococcus epidermidis*. *Rev Infect Dis* 1983;**5**: 543–8.

21 Slaughter L, Morris JF, Starr A. Prosthetic valvular endocarditis. A 12 year review. *Circulation* 1973;**47**: 1319–26.

22 Wilson WR, Jaumin PM, Danielson GK, *et al.* Prosthetic valve endocarditis. *Ann Intern Med* 1975;**82**: 751–6.

23 Saffle JR, Gardner P, Schoenbaum SC, Wild W. Prosthetic valve endocarditis. The case for prompt valve replacement. *J Thorac Cardiovasc Surg* 1977; **73**:416–20.

24 Lau JKH, Robles A, Cherian A, Ross DN. Surgical treatment of prosthetic endocarditis. Aortic root replacement using a homograft. *J Thorac Cardiovasc Surg* 1984;**87**:712–6.

25 Donaldson RM, Ross DN Homograft aortic root replacement for complicated prosthetic valve endocarditis. *Circulation* 1984;**70**:178–81.

26 Raychaudhury T, Cameron EWJ, Walbaum PR. Surgical management of prosthetic valve endocarditis. *J Thorac Cardiovasc Surg* 1983;**86**:112–4.

27 Baumgartner WA, Miller C, Reitz BA, *et al.* Surgical treatment of prosthetic valve endocarditis. *Ann Thorac Surg* 1983;**35**:87–104.

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Prosthetic valve endocarditis

A survey

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SUMMARY Fifty eight patients (aged 8–59 years, mean 27) treated for prosthetic valve endocarditis from January 1966 to January 1985 were studied retrospectively by review of case notes. There were 12 cases of early and 46 cases of late prosthetic valve endocarditis. These developed in 28 patients with an isolated aortic valve, in 26 with an isolated mitral valve, and in four with both aortic and mitral prosthetic valves. Streptococci were the most commonly isolated micro-organisms, followed by staphylococci, Gram negative bacteria, and fungi. A surgical (34 cases) or a necropsy specimen (10 cases) from 44 cases was examined. Eighty two per cent of the patients had congestive heart failure. Twenty four of the 58 patients were medically treated and 17 died (70% mortality). Combined medical and surgical treatment was used in 34 patients; the main indication for surgery was congestive heart failure. Fourteen patients on combined treatment died (40% mortality). Persistent sepsis and prosthetic valve dehiscence were the most common early and late operative complications. The most important influences on outcome were congestive heart failure, the type of micro-organism, the severity and extent of anatomical lesions, the time of onset of prosthetic valve endocarditis, and the type of treatment.

This survey indicates that only patients without congestive heart failure or embolic complications and with sensitive micro-organism should be treated medically. In view of the poor prognosis patients with prosthetic valve endocarditis associated with congestive heart failure, persistent sepsis, and repeat arterial emboli should be treated by early surgical intervention.

Despite advances in antimicrobial treatment and in surgical management, postoperative endocarditis still causes considerable morbidity and mortality in patients with prosthetic heart valves. We examined the clinical course and treatment of 58 patients with prosthetic valves who presented with endocarditis over a 15 year period (1968–84).

Patients and methods

Patients treated for prosthetic valve endocarditis from January 1966 to December 1984 were studied retrospectively by review of case notes.

The diagnosis of prosthetic valve endocarditis was established by the presence of one or both of the following criteria: histopathological evidence of endocarditis in a surgical or necropsy specimen; at least two blood cultures that were positive for the same organism and associated with an obvious clinical picture of prosthetic valve endocarditis, valve dysfunction, or signs of septic emboli. Endocarditis diagnosed within 60 days of operation was classified as early, cases presenting beyond this time were classified as late endocarditis. The term active prosthetic valve endocarditis included patients with positive blood cultures in the 48 hours before surgical intervention, a prosthesis giving a positive culture, or a myocardial abscess found at operation or necropsy. We used the χ^2 test for statistical analysis.

Results

Prosthetic valve endocarditis developed in 58 (5 9%) (38 M, 24 F) of 979 patients with cardiac valve replacement followed by us at our hospital between January 1968 and December 1984. The age range of these 58 patients was 8–59 years (mean 27 years). There were 12 cases of early and 46 of late

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prosthetic valve endocarditis. Endocarditis developed in 28 patients with an aortic valve, in 26 with a mitral valve, and in four with combined aortic and mitral valve replacement.

CLINICAL CHARACTERISTICS

Fever was the most common clinical finding (55 (95%)). Other physical signs were splenomegaly (10 (17%)) and cutaneous signs (11 (18%)). Anaemia, with haematocrit of $<35\%$ and increased white cell count was detected in 50%; 28% had haematuria and 16% had proteinuria. Nearly all the patients had an increased erythrocyte sedimentation rate.

MICROBIOLOGY

Table 1 shows the micro-organisms that caused prosthetic valve endocarditis in this study. These were identified by blood cultures from 34 (59%) patients. Streptococci were the most commonly isolated organism, followed by staphylococci, Gram negative bacteria, and fungi. Twenty four (41%) patients had negative blood cultures. Streptococci were more common in late prosthetic valve endocarditis, whereas more antibiotic resistant micro-organisms (staphylococci, Gram negative bacteria) were more common in early prosthetic valve endocarditis. Table 2 shows the likely sources of infection in 36 (62%) patients. Portals of entry were different in early and late prosthetic valve endocarditis; in late prosthetic valve endocarditis dental treatment (usually without antibiotic prophylaxis) was the most common factor indentified, followed by genital and urinary tract infection. Infections causing early prosthetic valve endocarditis occurred mainly during cardiopulmonary bypass or in the early post-operative period (11/12 cases). Immunological investigations were performed in only four patients.

ECHOCARDIOGRAPHY

Echocardiography was performed in 18 patients. Dehiscence of the prosthetic device was seen in two patients with aortic valve replacement and vegetations in three patients also with prosthetic aortic valves.

Table 1 *Microbiological causes of prosthetic valve endocarditis (PVE) in 58 patients (12 early cases and 46 late cases)*

Micro-organism	*No of patients*				
	Early PVE (12)		*Late PVE (46)*		*Total (58)*
Streptococcus		1		13	14 (24%)
Staphylococcus					
S epidermidis	2		3		10 (17%)
S aureus	2		3		
		6		14	
Gram negative bacteria	2		7		9 (15 5%)
Candida albicans	0		1		1 (1 7%)
Negative blood culture		5		19	24 (41%)

PATHOLOGICAL CHANGES

Examination of surgical (34 cases) or necropsy specimens (10 cases) found abnormalities in 26 aortic and 21 mitral prostheses (table 3). The most common lesions were dehiscence (36/44) and vegetations (33/44); thromboses were more common on mitral prostheses than on aortic prostheses. The valve ring was usually considerably altered and extension of the infection to the adjacent cardiac structures was common. In the three bioprostheses that were examined infection affected the valve leaflets but not adjacent host tissue.

COMPLICATIONS

Congestive heart failure occurred in 48 patients (82%) (12 early and 36 late cases of prosthetic valve endocarditis), neurological complications in 15 (25%) (13 embolic strokes and two cerebral abscesses) (three early and 12 late cases of prosthetic valve endocarditis), and peripheral vascular emboli in 27 patients (46%) (three early and 24 late cases of prosthetic valve endocarditis).

Fever persisted in 21 patients (nine early and 12 late prosthetic valve endocarditis) after the start of appropriate medical treatment, and atrioventricular conduction disturbances with complete heart block, related to extension of the infection to the conduction system, were seen in three patients with late prosthetic valve endocarditis; six (10%) patients with prosthetic valve endocarditis (all late cases) had renal failure.

TREATMENT AND OUTCOME

Twenty four patients had medical treatment alone; seven survived. Thirty four patients had combined medical and surgical treatment (table 4). Twenty three patients were operated on in France and 11 in Tunis.

Table 2 *Sources of infection in 36 patients with prosthetic valve endocarditis (PVE)*

Portal of entry	*Early PVE*	*Late PVE*	*Total*
Dental treatment	1	6	7
Cutaneous infection		1	1
Urinary tract infection		4	4
Pulmonary infection		4	4
Genital infection		5	5
Gastric infection		2	2
Caesarean section		1	1
Post-cardiopulmonary bypass	11		11

Table 3 *Pathological findings in 26 aortic and 21 mitral prostheses or bioprostheses seen at operation (34 cases) or at necropsy (10 cases)*

Finding	*Aortic replacement (26)*	*Mitral replacement (21)*	*Total (44)*	%
Valve dehiscence	20	16	36	82
Vegetations	18	15	33	75
Thrombosis	2	9	11	25
Ring valve abscess	12	4	16	36
Complete destruction of ring valve	2	1	3	7
Aortic aneurysm	4	—	4	9
Myocardial abscess	2	1	3	7
Septal involvement	2	1	3	7
Aortic abscess	1	—	1	2
Torn valve leaflets*	2	1	3	7
Extension of infection to adjacent cardiac structures	16	7	23	

*Bioprostheses.

RESULTS OF MEDICAL TREATMENT

Of the seven patients who survived after medical treatment (one with early prosthetic valve endocarditis and six with late prosthetic valve endocarditis), two were lost to follow up and five were followed for 6–120 months (mean 64 months); all of them are alive and well—one is in grade I and four in grade II of the New York Heart Association classification. The patients were not treated surgically because they responded well to medical treatment and had no obvious signs of cardiac failure or valve dysfunction. Seventeen (70%) of the medically treated patients died. We attribute this high mortality to the fact that patients treated medically were usually referred from other hospitals, they were already critically ill, with congestive heart failure, low cardiac output, and sometimes neurological disturbances, and were too ill to undergo operation. The main cause of death was prosthetic valve dysfunction or cardiac failure or both in 11 patients; neurological complications with coma was the cause of death in five patients; and persistent sepsis in one patient.

Table 4 *Outcome in 58 patients with prosthetic valve endocarditis*

Treatment	*Total No (%)*	*Survived No (%)*	*Died No (%)*
Medical/antibiotics alone	24 (42)	7 (29)	17 (71)
Medical and surgical (antibiotics + reoperation)	34 (58)	20 (59)	14 (41)
Total	58	27	31

Table 5 *Indications for surgical treatment of infected prosthetic valves*

Indications	*No patients*	%
Cardiac failure (prosthetic dysfunction)	19	56
Cardiac failure and persistent sepsis	14	41
Fungal PVE	1	3

PVE, prosthetic valve endocarditis

RESULTS OF COMBINED MEDICAL AND SURGICAL TREATMENT

Thirty four of the 58 patients underwent repeat operation because of prosthetic valve endocarditis, and in some instances further operations were required. Thirty had late prosthetic valve endocarditis and four had early prosthetic valve endocarditis. Fifteen were operated on during an active stage. Table 5 lists the indications for operation in patients with infected prosthetic valves.

The main indication for surgery was progressive severe congestive heart failure caused by valve dysfunction, with or without persistent sepsis. One patient with *Candida albicans* infection of a Björk mitral valve died postoperatively of low cardiac output. In all cases operation included debridement of infected tissue. In four partial valve dehiscence was repaired without valve replacement; in 30 cases, correction of a haemodynamically important paravalvar leak had to be done by valve replacement, with reconstruction of aortic annulus in six cases, supra-annular insertion of aortic prosthesis associated with coronary bypass in two cases, and insertion of a mitral prosthesis inside the atrial cavity in two cases.

OPERATIVE MORTALITY

Fourteen (41%) patients died: nine from low cardiac output, three from neurological complications, one from severe septicaemia, and one from ventricular arrhythmias.

Many of the 20 patients who survived had early postoperative complications (table 6). The most frequent were persistent sepsis (5) and early prosthetic valve dehiscence (6) (three because of infection and three mechanical failures); three had a repeat valve replacement—one survived and two died. There

Table 6 *Early postoperative complications in 20 survivors two months after operation for prosthetic valve endocarditis (PVE)*

Complications	*No patients*	%
Persistent sepsis:	5	25%
Staphylococcus	2	
Gram negative bacteria	1	
Candida albicans	1	
Negative blood culture	1	
Early prosthetic valve dehiscence	6*	30%
Infection	3	
Mechanical	3	
Cerebral emboli	2	35%
Ventricular arrhythmia	2	
Complete heart block	2	
Mediastinal infection	1	

*Three recurrent valve replacement, two deaths, and one survivor.

were two types of major complications in the 18 patients who survived for more than two months after operation: persistent sepsis (3) (two survived and one died after repeat prosthetic valve replacement because of major valve dehiscence) and late prosthetic or periprosthetic leak (6) (two minor and four major requiring subsequent reoperation with three deaths from low cardiac output.

So 14 are alive after operation. Eleven were followed (six with aortic and five with mitral valve replacement) (table 7).

PROGNOSIS

We compared the 16 survivors with the 37 patients who died (table 8) to determine what factors were important to outcome. Five patients were lost to follow up (three survivors with combined medical and surgical treatment and two survivors with medical treatment). Congestive heart failure occurred in 94% (35/37) of those who died and in 50% (8/16) of survivors ($p < 0{\cdot}01$).

Seventy eight per cent (11/14) of patients with bacteria sensitive to antibiotics survived and 21% (3/14) died; whereas 20% (4/20) of patients with resistant bacteria survived and 80% (16/20) died ($p < 0{\cdot}025$).

Outcome was better when infection was restricted to the prostheses (13/21) or 61% mortality compared with 86% (20/23) mortality in extensive lesions.

Mortality from early prosthetic valve endocarditis was much higher (11/11) than that in patients with late prosthetic valve endocarditis (61% (26/42)).

A combination of medical and surgical treatment was associated with a slight improvement in outcome: 35% (11/31) *vs* 22% (5/22) in the medically treated group ($p < 0{\cdot}05$).

Mortality in patients with neurological complications (74%) was not different from that in patients without such complications (72%).

Table 7 *Clinical results in 11 survivors after surgical treatment for prosthetic valve endocarditis. Follow up period 18–62 months (mean 41 months)*

Result	*NYHA grade*	*CTR*	*ECG*	*Aortic (6)*	*Mitral (5)*
Excellent	I–II	Normal	Normal		1
Good	I–II	Increased	Moderately altered	6	4

CTR, cardiothoracic ratio, NYHA, New York Heart Association.

Table 8 χ^2 *test to compare mortality and survival associated with various prognostic features*

	Survivors (16)	*Deaths (37)*	χ^2 *test*
PVE with congestive heart failure	8	35	$p < 0{\cdot}01$
Sensitive bacteria	11	3	$p < 0{\cdot}025$
Resistant bacteria	4	16	
Active PVE	3	20	$p < 0{\cdot}05$
Healed PVE	13	17	
Infection localised to prostheses	8	13	$p < 0{\cdot}05$
Extension of infection to myocardium or wall of great vessels	3	20	
PVE with CNS complications	4	11	NS
PVE without CNS complications	12	26	
Early PVE	0	11	$p < 0{\cdot}01$
Late PVE	16	26	
Medical treatment	5	17	$p < 0{\cdot}05$
Combined medical surgical treatment	11	20	

CNS, central nervous system; PVE, prosthetic valve endocarditis.

Discussion

Prosthetic valve endocarditis is a serious and increasingly common complication of heart valve replacement; it is reported in 1–9, 4% of patients with prosthetic valve replacement.[1-5] The high overall frequency (5·9%) in our series may be the result of inadequate prophylaxis. Clinical diagnosis is established by fever, leucocytosis, haematuria, cutaneous signs, splenomegaly, and the discovery at auscultation of new regurgitant murmurs.[4 6] In 60% of our patients blood cultures were positive. The rate of negative blood cultures was high because many of our patients were referred from other hospitals and were already on antibiotics. Immunological abnormalities are a useful diagnostic feature in patients with negative blood cultures.[7-9]

Like other workers,[6 10-13] we too found that streptococci were the most common causal micro-organisms—followed by staphylococci, Gram negative bacteria, and fungi. Streptococci commonly cause late prosthetic valve endocarditis, often after treatment, whereas staphylococci, Gram negative bacteria, and *Candida* species are more important in early prosthetic valve endocarditis.[3 6 14] The organisms are mainly acquired in the operating rooms or in the intensive care unit.[3]

There are differences in pathological findings between mechanical valves and bioprosthetic valves. In mechanical valves endocarditis is often associated with an infection behind the site of attachment of the prosthesis, resulting in ring abscess and dehiscence of the prosthesis.[15] Extension of infection to adjacent cardiac structures is very common and it may cause a myocardial abscess, disruption of the atrioventricular conduction system, or fistulas into the right heart or pericardium.[15] Vegetations are also common and they can be extensive, particularly in fungal infection. Ferrans *et al* found that bioprosthetic infection is usually localised to the cusps.[16]

Renal failure and nephrotic syndrome are rare,[17] and due to a focal or diffuse glomerlonephritis and associated with immune complex in the serum and immunoglobulin deposits on the capillary wall.[18]

Mortality from prosthetic valve endocarditis is high, ranging from 35% to 71%.[1 3-5 11-13] A new or an increased regurgitant murmur and the presence of congestive heart failure[4 6] are associated with a very high mortality. We found 95% mortality in patients with heart failure compared with 50% in patients without congestive heart failure. The type of micro-organism is a major factor; patients with prosthetic valve endocarditis caused by less pathogenic organisms that are susceptible to antibiotic treatment respond better than those with prosthetic valve endocarditis caused by more invasive, antibiotic resistant bacteria.[4 6 11] In the present series the mortality rate in streptococcal prosthetic valve endocarditis was 21% compared with 80% in non-streptococcal prosthetic valve endocarditis.

Extension of infection into the valve seat and adjacent tissues may result in partial or complete valve dehiscence, myocardial abscess, disruption of the atrioventricular conduction system, or fistulas into the right heart or pericardium. Our results and those of others[6 19 20] suggest that invasion of the myocardium is associated with an increased mortality.

Mortality also varies with the time of onset of prosthetic valve endocarditis; most reports emphasise that prognosis is better in late prosthetic valve endocarditis[6 10 12 13] than in early infection.[11 20 21] This difference may be attributed to the predominance of streptococcal infection in late prosthetic valve endocarditis and the more pathogenic organisms seen in early prosthetic valve endocarditis, to immediate recovery from the operation, and to altered host resistance produced by the pump oxygenator.[22 23] Neurological complications are an important cause of mortality and morbidity.[6] Twenty five of the 33 deaths reported by Masur and Johnson were attributed to cardiac causes and eight to central nervous system events.[4]

Operation has dramatically improved the prognosis of prosthetic valve endocarditis. Gardner *et al* combined the results of treatment for prosthetic valve endocarditis of three published series and demonstrated a higher survival rate with combined valve replacement and antibiotic treatment compared with medical treatment alone.[24] Stinson *et al* successfully treated 12 of 17 patients with active prosthetic valve endocarditis by combined valve replacement and antimicrobial treatment; operative mortality was 24%.[25] These investigators recommend intervention irrespective of the stage of endocarditis.

Medical treatment alone should be used only in cases of prosthetic valve endocarditis caused by antibiotic sensitive micro-organisms, with unimportant or no prosthetic dysfunction, and when congestive heart failure and embolic events are absent.[26] Early operation combined with antibiotic treatment should be considered in all other cases.[6 25] The main indications for operation are listed below: (*a*) Congestive heart failure with coexistent prosthetic dysfunction that does not respond to medical treatment.[13 27] (*b*) Persistent sepsis after 7–10 days of appropriate antibiotic treatment or relapse after appropriate treatment or when fungal endocarditis is diagnosed. (*c*) Occurrence of an arterial embolus when echocardiography demonstrates residual vegetations[13] or in the absence of abnormal echocardiographic findings when more than one arterial embolus occurs, or the presence of a single embolus which if exacerbated by a further embolic insult might result in irreversible neurological damage.[6 12 19] (*d*) Conduction system abnormalities almost always indicate an annular abscess with extension to the septum[13] and such lesions do not respond to medical treatment.[19 28] (*e*) The appearance of new murmurs caused by fistulas into the right heart or pericardium or by septal rupture.[26]

Conclusion

The high mortality in prosthetic valve endocarditis is mainly the result of congestive heart failure which is usually caused by prosthetic valve dysfunction. Mortality in early and late prosthetic valve endocarditis is reduced by prompt surgical intervention and adequate antibiotic treatment.

References

1 Anger P, Marquis G, Dyrda I, Martineau JP, Solymoss CB. Infective endocarditis update experience from a heart hospital. *Acta Cardiol (Brux)* 1981;2:105–23.

2 Calderwood SB, Swinski LA, Waternaux CM, Karchmer AW, Buckley MJ. Risk factors for the development of prosthetic valve endocarditis. *Circulation* 1985;1:31–7.

3 Ivert TA, Dismukes WE, Cobbs CG, Blackstone EH, Kirklin JW, Bergdahl LAL. Prosthetic valve endocarditis. *Circulation* 1984;2:223–32.

4 Masur H, Johnson WD. Prosthetic valve endocarditis. *J Thorac Cardiovasc Surg* 1980;**80**:31–7.

5 Vahanian A, Prost JF, Richard C, Dewilde J, Acar J. Endocardites infectieuses chez les porteurs de prothèses valvulaires. *Arch Mal Coeur* 1982;75: 971–9.

6 Karchmer AW, Dismukes WE, Buckley MJ, Austen WG. Late prosthetic valve endocarditis. Clinical features influencing therapy. *Am J Med* 1978;**64**: 199–206.

7 Carson DA, Bayer AS, Eisenberg RA, Lawrence S, Theofilopoulos AN. IgG rheumatoid factor in subacute bacterial endocarditis: relationship to IgM rheumatoid factor and circulating immune complexes. *Clin Exp Immunol* 1978;**31**:100–3.

8 Herreman G, Godeau P, Cabane J, Digeon M, Bach JF. Complexes immuns circulants et endocardites infectieuses. A propos de 64 observations. *Ann Med Interne (Paris)* 1978;**129**:387–97.

9 Ben Ismail M, Hannachi N. *Etude immunologique des endocardites infectieuses et du rhumatisme articulaire aigu*. Tunis: Editions Techniques Spécialisées 1984.

10 Baumgartner WA, Miller DC, Reitz BA, *et al*. Surgical treatment of prosthetic valve endocarditis. *Ann Thorac Surg* 1983;**35**:87–104.

11 Rossiter SG, Stinson EB, Oyer PE, *et al*. Prosthetic valve endocarditis. Comparison of heterograft tissue valves and mechanical valves. *J Thorac Cardiovasc Surg* 1978;**76**:795–803.

12 Slaughter L, Morris JE, Starr A. Prosthetic valvular endocarditis: a 12 year review. *Circulation* 1973;**47**: 1319–26.

13 Wilson WR, Jaumin PM, Danielson GK, Giuliana ER, Washington JA, Geraci JE. Prosthetic valve endocarditis. *Ann Intern Med* 1975;**82**:751–6.

14 Sweeney MS, Reul GJ, Cooley DA, *et al*. Comparison of bioprosthetic and mechanical valve replacement for active endocarditis. *J Thorac Cardiovasc Surg* 1985;**90**:676–80.

15 Mayer KH, Schoenbaum SC. Evaluation et conduite à tenir dans l'endocardite sur prothèses valvulaires *Acquisitions Nouvelles en Pathologie Cardiovasculaire* 1983;**25**:59–79.

16 Ferrans VJ, Boyce SW, Billingham ME. Infection of gluteraldehyde—preserved porcine valve heterografts. *Am J Cardiol* 1979;**43**:1123–34.

17 Witchitz S. Les endocardites infectieuses. *Encycl Med Chirug Paris Coeur* 11009,A.10,9.

18 Morel Maroger L, Sraer JD, Herreman G, Godeau P. Kidney in subacute endocarditis; pathological and immunofluorescence findings. *Arch Pathol* 1972;**94**: 205–13.

19 Arnett EN, Roberts WC. Prosthetic valve endocarditis. A study of 18 patients at necropsy. *Am J Cardiol* 1975;**35**:120.

20 Madison J, Wang K, Gobel FL, Edwards JE. Prosthetic aortic valvular endocarditis. *Circulation* 1975;**51**:940–9.

21 Dismukes WE, Karchmer AW, Buckley MJ, Austen WG, Swarts MN. Prosthetic valve endocarditis. An analysis of 38 cases. *Circulation* 1973;**48**:365–77.

22 Nunez L, de la Liana R, Auguado MG, Iglesias A, Larrea JL, Celemin D. Bioprosthetic valve endocarditis, indicators for surgical intervention. *Ann Thorac Surg* 1983;**35**:262–70.

23 Magilligan D Jr, Quinn EL, Davila JC. Bacteremia endocarditis and the Hancock valve. *Ann Thorac Surg* 1977;**24**:508–18.

24 Gardner P, Saffle Jr, Shoenbaum SC. Management of prosthetic valve endocarditis. In: Duma RJ, ed. *Infections of prosthetic valves and vascular grafts: prevention, diagnosis and treatment*. Baltimore: University Park Press, 1977:123.

25 Stinson EB, Griepp RB, Vosti K, Copeland JG, Shumway NE. Operative treatment of active endocarditis. *J Thorac Cardiovasc Surg* 1976;**71**:659–65.

26 Ben Ismail M, Abid F, Hannachi N, Boughzela E. Les endocardites infectieuses sur prothèses valvulaires. Jean ACAR; Cardiopathies valvulaires acquises 1985. Paris: Flammarion. Medecine—Sciences 1985:630–6.

27 Johnson WD Jr. Prosthetic valve endocarditis In: Kaye D, ed. *Infective endocarditis*. Baltimore: University Park Press, 1976:129–42.

28 Anderson DJ, Bulkley BH, Hutchins GM. A clinico pathologic study of prosthetic valve endocarditis in 22 patients: morphologic basis for diagnosis and therapy. *Am Heart J* 1977;**94**:325–32.

Br Heart J 1987;58:78–81

Case reports

Rupture of a saphenous vein bypass graft during coronary angioplasty

ERIC DRUMMER, KEVIN FUREY, JAY HOLLMAN

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SUMMARY A self-limited rupture of a five month old saphenous vein bypass graft occurred during coronary angioplasty when the balloon used to stretch the vessel proved to be too large. A lack of fibrous tissue in the new graft may have predisposed it to rupture.

Percutaneous transluminal coronary angioplasty has been used to treat obstructions of the saphenous vein graft anastomosis or of the vein body itself.[1-5] Rupture and perforation of coronary arteries during angioplasty is rare.[6-11] Rupture or perforation of saphenous vein bypass grafts has not been described. We report a case of rupture of a saphenous vein bypass graft during percutaneous transluminal coronary angioplasty.

Case report

This 47 year old hypertensive man had first complained of angina pectoris five years before percutaneous transluminal coronary angioplasty. The angina was progressive and eventually chest pain at rest developed. This was relieved by nitrates. The patient then underwent coronary artery bypass surgery to the left anterior descending artery, right coronary artery, and circumflex coronary artery. He did well until angina recurred a month before the present admission. Initially, he only had angina with moderate exertion, but this progressed to episodes during minimal exertion and at rest. Repeat cardiac catheterisation demonstrated that the grafts to the circumflex and right coronary arteries were widely patent. The saphenous vein graft to the left anterior descending artery had a long segment of smooth narrowing of 95–99% with slow anterograde filling of the distal native left anterior descending artery (fig 1).

Angioplasty was attempted with a 9 French El Gamal guiding catheter and a 4 mm USCI low profile balloon (United States Catheter and Instrument Corporation, Billerica, MA). The balloon was passed over a 0·018 inch high torque floppy ACS guide wire (Advanced Cardiovascular Systems, Mountain View, CA). There was no difficulty negotiating the obstruction and in passing the guide wire to the distal portion of the left anterior descending coronary artery. The balloon was then inflated four times to a maximum pressure of 8 atmospheres for a maximum of 60 seconds. At 8 atmospheres, the ratio of the inflated balloon to the distal artery was 1·22/1, and the balloon slightly overdistended the distal vein. During balloon inflations the patient had transient angina pectoris associated with 1 mm ST segment depression in lead V5. The initial transstenotic gradient across the lesion was 60 mm Hg and this was reduced to 4 mm Hg after coronary angioplasty. After the last balloon inflation the patient continued to have mild residual chest discomfort which was unlike his angina pectoris. This was not associated with any ST segment changes on his electrocardiogram. After removal of the balloon, angiograms revealed that the area of the saphenous vein graft obstruction was widely patent with slight residual narrowing. There was extravasation of contrast material outside the wall of the vein, however, which continued proximally in a linear fashion along the vein in a sinus tract (fig 2). Repeat fluoroscopic examination of this area showed that the dye remained in this extraluminal area for the 45 minute observation period in the laboratory. The patient's blood pressure and heart rate remained stable and a Swan-Ganz catheter was inserted to monitor haemodynamic variables: initial pulmonary artery pressure 16/6 mm Hg (mean 8 mm Hg); mean pulmonary capillary wedge pressure 2 mm Hg; and mean right atrial pressure 1 mm Hg. The patient was transferred to the cardiac care unit for continued monitoring. The patient did well and had no appreciable increase in his right heart pressures and no

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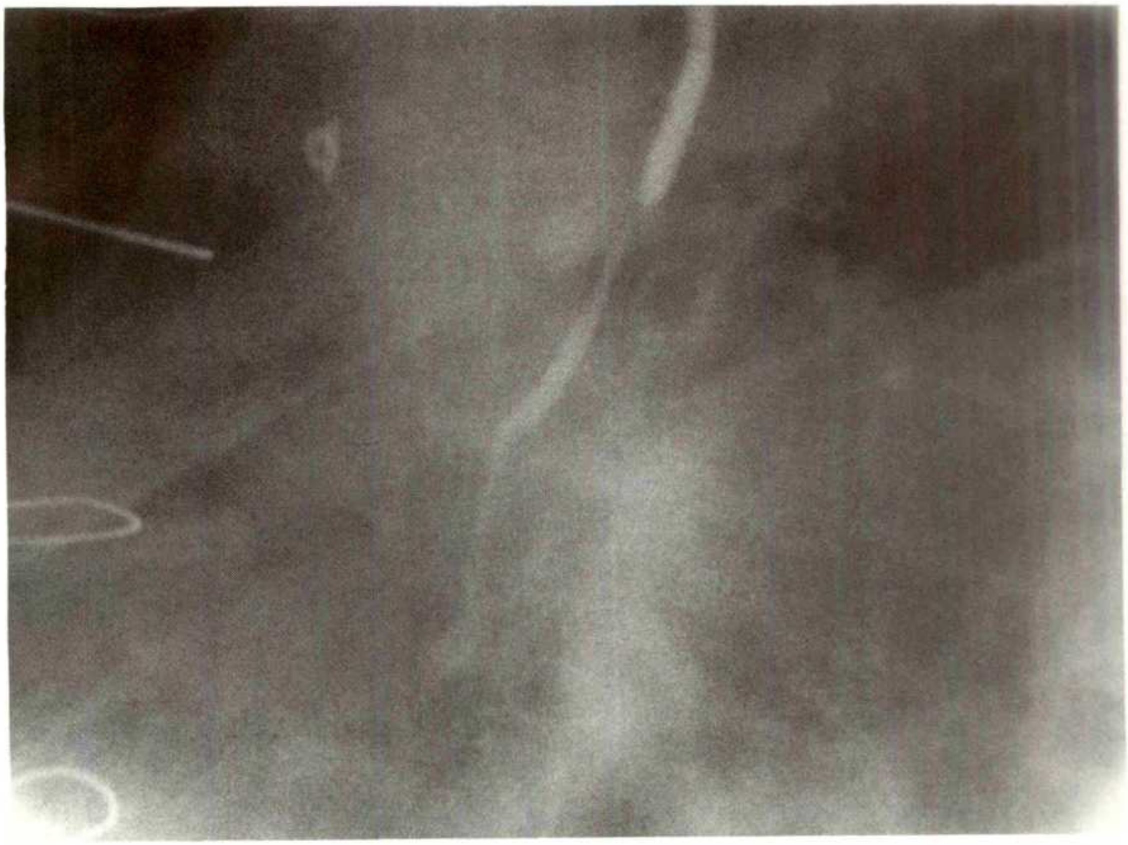

Fig 1 *Angiogram in the left anterior oblique projection with craniocaudal angulation showing saphenous vein graft to the left anterior descending coronary artery. There was severe narrowing in the vein just before the distal anastomosis and slow anterograde filling of the distal left anterior descending coronary artery.*

important change in vital signs. Repeat fluoroscopy the next day did not show residual contrast material at the area of the extravasation. At no time did any signs of cardiac tamponade develop. The patient's non-anginal chest pain resolved approximately two to three hours after the procedure and he was discharged from the hospital on the third hospital day. Four months after angioplasty he is active and free of angina.

Discussion

The most common coronary vascular complications of angioplasty are dissection, acute occlusion, and spasm. A recent series of patients indicates that this occurs in approximately 5% of cases.[6 8] Perforation of the native coronary arteries is rare, but it has been described in several case reports.[7 9-11] Perforation was usually caused by passage of a guide wire into a false channel and this can cause cardiac tamponade or may not have any adverse effects. Rupture of the native coronary artery after safe passage of the balloon is rare. It has been reported twice.[7 9] In both cases rupture of the coronary artery was thought to have been caused by the use of a balloon that was too large for the size of the artery. When a small diagonal vessel was affected the clinical course was not life threatening,[9] but balloon rupture of a dominant right coronary artery resulted in pericardial tamponade, progressive hypotension, and death.

In our case a five month old saphenous vein graft was ruptured. Rupture was self-limited and had no adverse outcome. The ratio of the inflated balloon diameter to the vessel diameter was 1·22/1. The diameter of the inflated balloon was not too large for the size of the distal artery or for dilatation of native arteries.[12] Dorros has proposed the use of 4·2 and 5·0 mm balloons in saphenous vein angioplasty to reduce the recurrence rate.[13] This vein graft had only been in place for five months, however. It is

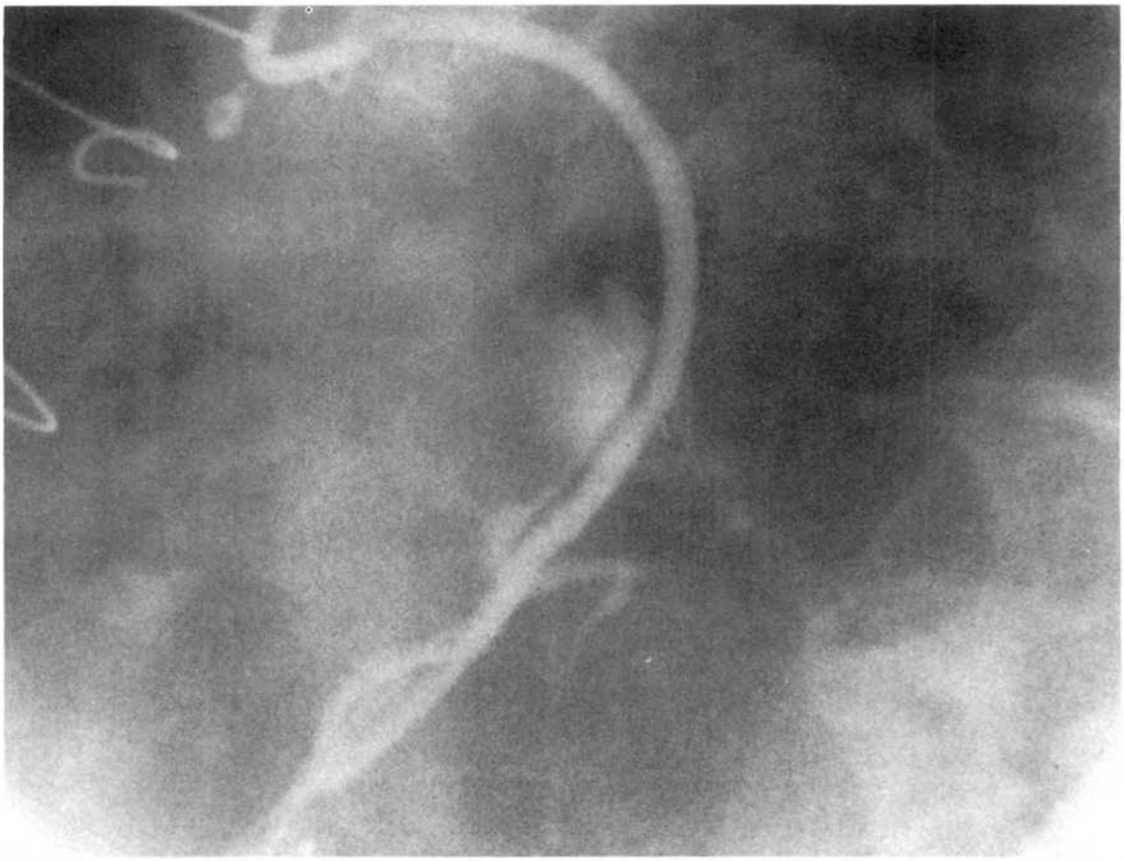

Fig 2 *Angiogram in the left anterior oblique projection with craniocaudal angulation obtained after angioplasty. There was slight residual narrowing in the area of obstruction and extravasation of dye outside the wall of the vein, which appeared to travel along the vein in a sinus tract.*

known that fibrosis of the walls of a vein graft takes time to develop.[14] The longer the vein graft is in place, the greater the replacement of smooth muscle cells by fibrous elements in the media and adventitia. If fibrosis of the vein has not had time to develop, the vein may be more susceptible to rupture if a large balloon is used.

The presence of chest pain and the absence of extensive haemorrhage into the chest are two other interesting aspects of this case. The constancy of the pain in the absence of electrocardiographic changes suggests that it originated in the pericardium or arterial wall. Pericarditic chest pain sometimes follows angioplasty.[15] Even in the absence of arterial perforation, patients may show arterial haemorrhage over the dilated native arteries at subsequent operation for elective or emergency bypass surgery. Presumably, this haemorrhage can cause pericardial irritation and pericarditic chest pain.

The patient showed no signs of pericardial tamponade or extensive blood loss despite clear rupture of the vessel. The dye appeared to be contained in a tissue sac surrounding the vein. This presumably was connective tissue; such tissue is often seen at reoperation, densely adhering to the vein structure. In this patient it must have prevented tamponade or serious intrathoracic haemorrhage.

References

1 Ford WB, Wholey MH, Zikria EA, Somadani SR, Sullivan ME. Percutaneous transluminal dilatation of aortocoronary saphenous vein bypass grafts. *Chest* 1981;**79**:529–35.

2 Douglas JS, Gruentzig AR, King SB, *et al.* Percutaneous transluminal coronary angioplasty in patients with prior coronary bypass surgery. *J Am Coll Cardiol* 1983;**2**:745–54.

3 El Gamal M, Bonnier H, Michels R, Heijman J, Stassen E. Percutaneous transluminal angioplasty of

stenosed aortocoronary bypass grafts. *Br Heart J* 1984;**52**:617–20.

4 Corbelli J, Franco I, Hollman J, Simpfendorfer C, Galan K. Percutaneous transluminal coronary angioplasty after previous coronary artery bypass surgery. *Am J Cardiol* 1985;**56**:398–403.

5 Reeder GS, Bresnahan JF, Holmes DR, *et al.* Angioplasty for aortocoronary bypass graft stenosis. *Mayo Clin Proc* 1986;**61**:14–9.

6 Bredlau CE, Roubin GS, Leimgruber PP, Douglas JS, King SB, Gruentzig AR. In-hospital morbidity and mortality in patients undergoing elective coronary angioplasty. *Circulation* 1985;**72**:1044–52.

7 Saffitz JE, Rose TE, Oaks JB, Roberts WC. Coronary arterial rupture during coronary angioplasty. *Am J Cardiol* 1983;**51**:902–4.

8 Cowley MJ, Darros G, Kelsey SF, Van Raden M, Detre KM. Acute coronary events associated with percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1984;**53**:12C–6C.

9 Meier B. Benign coronary perforation during percutaneous transluminal coronary angioplasty. *Br Heart J* 1985;**54**:33–5.

10 Grollier G, Bories H, Commeau P, Foucault JP, Potier JC. Coronary artery perforation during coronary angioplasty. *Clin Cardiol* 1986;**9**:27–9.

11 Kimbiris D, Iskandrian AS, Goel I, *et al.* Transluminal coronary angioplasty complicated by coronary artery perforation. *Cathet Cardiovasc Diagn* 1982;**8**:481–7.

12 Roubin GS, Leimgruber PP, Whitworth HB, *et al.* Influence of balloon size on outcome after coronary angioplasty (PTCA) [Abstract]. *Circulation* 1986; **72**(suppl II):400.

13 Dorros G. Coronary and/or saphenous vein graft angioplasty in patients with prior coronary artery bypass graft surgery. In: Ischinger T, ed. *Practice of coronary angioplasty.* New York: Springer-Verlag, 1986:267–83.

14 Spray TL, Roberts WC. Changes in saphenous veins used as aortocoronary bypass grafts. *Am Heart J* 1977;**94**:500–16.

15 Slack JD, Pinkerton CA, Nasser WK. Acute pericarditis after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1985;**55**:843–4.

Br Heart J 1987;**58**:82–4

Spontaneous resolution of a dissection of the descending aorta after medical treatment with a β blocker and a calcium antagonist

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SUMMARY A 58 year old man experienced an attack of squeezing chest pain. A contrast enhanced computed tomographic scan showed acute dissection of the descending aorta. Treatment with metoprolol and nicardipine kept his blood pressure below 130/90 mm Hg while he was supine at rest and after walking. Serial contrast enhanced computed tomographic scans showed opacification of the false lumen (which was not opacified initially) on the 42nd day; moderate regression of the false lumen on the 67th day, and resolution of the false lumen on the 266th day.

This is the first in vivo demonstration of spontaneous resolution of aortic dissection detected by serial contrast enhanced computed tomographic scans.

Healing of an aortic dissection, particularly when thrombosis and organisation have obliterated the dissected segment, is rare and there are only a few necropsy reports of this finding.[1] Computed tomographic scanning has recently enhanced the rapidity and accuracy of diagnosis of aortic dissection.[2-4] We report the first case in which spontaneous resolution of the false lumen of aortic dissection was demonstrated in life by serial contrast enhanced computed tomographic scans after medical treatment with a β blocker and a calcium antagonist.

Case report

A 58 year old man suffered from an attack of squeezing chest pain in the morning while he was working in his garden. His blood pressure was 220/180 mm Hg. A dull chest pain persisted for more than a week after the attack. A contrast enhanced computed tomographic scan on the 13th day disclosed an acute dissection of the descending aorta to a level near the origin of the renal arteries. The false lumen was not opacified (fig 1). A chest *x* ray showed a wide aortic shadow. The electrocardiogram was normal. Routine laboratory tests were unremarkable except for a high erythrocyte sedimentation rate. He was examined repeatedly by computed tomographic scans and chest *x* rays His blood pressure while supine at rest and after walking was maintained below 130/90 mm Hg with metoprolol and nicardipine. He was free from chest pain soon after the start of this treatment. A contrast enhanced computed tomographic scan on the 42nd day showed that the false lumen was opacified to the same degree as the true lumen. Another scan on the 67th day revealed moderate regression of the false lumen. On the 266th day a contrast enhanced computed tomographic scan showed resolution of the false lumen with a thin residual thrombi in the dissected aortic wall (fig 2). A concomitant chest *x* ray showed that since the initial examination there had been a decrease in the width of the aortic shadow and the thickness of the aortic wall measured from the calcific intima to the outer margin of the aortic shadow. The high erythrocyte sedimentation rate declined gradually over the nine month period. A contrast enhanced computed tomographic scan and a chest *x* ray were unchanged a year later.

Discussion

Healing of aortic dissection is usually said to have occurred when the false lumen is endothelialised and communicates with the true lumen at both its origin and termination, forming a so called double aorta. Many cases of such a healing have been found at

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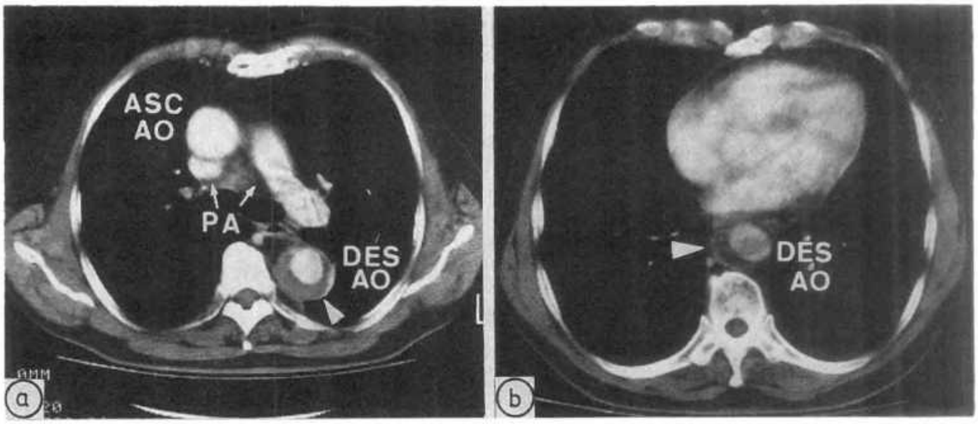

Fig 1 *Contrast enhanced computed tomographic scan of the thorax on the 13th day showing acute dissection of the descending aorta. The false lumen is not opacified. (a) Slice imaged at a level near the aortic arch and (b) a slice at a level about 6 cm below (a). ASC AO, ascending aorta; DES AO, descending aorta; PA, pulmonary arteries; arrowhead indicates false lumen.*

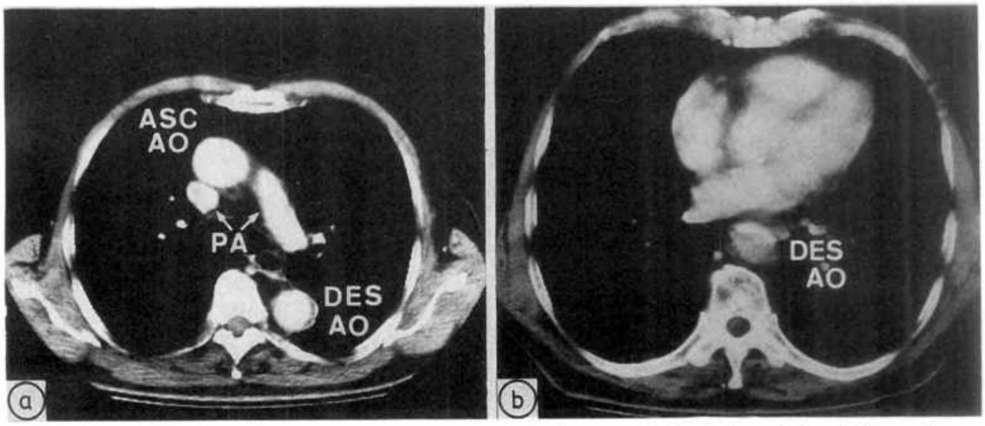

Fig 2 *Contrast enhanced computed tomographic scan of the thorax on the 266th day. (a) and (b) are the same views as described in fig 1. Resolution of the false lumen, with thin residual thrombi in the dissected segment, is evident.*

necropsy.[1] Healing produced by obliteration of the dissected segment by thrombosis and organisation is rare; there are only a few reports of this finding at necropsy.[5 6] We believe this to be the first in vivo demonstration of the spontaneous resolution of the false lumen of aortic dissection. The resolution was detected by serial contrast enhanced computed tomographic scans. Such scans are a rapid and accurate method of diagnosing aortic dissection[2-4] and seem to be more suitable than angiography for repeated follow up of patients with aortic dissection.

Medical treatment with a β blocker and a vasodilator to maintain blood pressure within normal limits and a suppressed cardiac inotropic state has been advocated in patients with uncomplicated dissection of the descending aorta.[4 7 8] Maintenance of normal and stable blood pressure, which in our case was achieved with a β blocker and a calcium antagonist, seems to have played a major role in the resolution of the false lumen. Location of the false lumen may also have had a favourable effect on such a healing. Dissection of the descending thoracic aorta usually produces a false lumen behind and to the left of the true lumen,[8] whereas in this case the false lumen lay behind and to the right of the true lumen. The spinal column may have acted as a buttress and may have prevented excessive expansion and rupture of the false lumen.

References

1 Hirst AE Jr, Johns VJ Jr, Kime SW Jr. Dissecting aneurysm of the aorta: a review of 505 cases. *Medicine (Baltimore)* 1958;37:217–79.
2 Godwin JD, Herfkens RL, Skioldebrand CG, Federle MP, Lipton MJ. Evaluation of dissections and aneurysms of the thoracic aorta by conventional and dynamic CT scanning. *Radiology* 1980;136·125–33.
3 Moncada R, Salinas M, Churchill R, *et al*. Diagnosis of dissecting aortic aneurysm by computed tomography. *Lancet* 1981;i:238–41.
4 Miller DC. Acute dissection of the aorta—continuing need for earlier diagnosis and treatment. *Mod Concepts Cardiovasc Dis* 1985;54.51–5.
5 Shennan T. Completely healed dissecting aneurysm of the aorta with obliteration of the sac. *J Pathol* 1932;35:161–74.
6 Case records of the Massachusetts General Hospital (Case 41091). *N Engl J Med* 1955;252:358–64.
7 Doroghazi RM, Slater EE, De Sanctis RW, Buckley MJ, Austen WG, Rosenthal S. Long-term survival of patients with treated aortic dissection. *J Am Coll Cardiol* 1984;3 1026–34.
8 Wheat MW Jr Acute dissecting aneurysms of the aorta: diagnosis and treatment—1979. *Am Heart J* 1980;99:373–87.

Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts will be 10 July 1987.

The Annual General Meeting for 1988 will take place in Belfast on 23 and 24 March 1988, and the closing date for receipt of abstracts will be 4 January 1988.

Interventional cardiology

An International Workshop on Future Directions in Interventional Cardiology, sponsored by the American College of Cardiology, with Santa Barbara Heart and Lung Institute at Goleta Valley Community Hospital, will be held in Santa Barbara on 25 to 27 September 1987. Further information from: Ms Lan Nguyen/1638A, Extramural Programs Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20814, USA.

Cardiac Doppler and color flow imaging

An International Conference on Cardiac Doppler and Color Flow Imaging will be held in Dubrovnik on 29 May to 2 June 1988. Inquiries to Dr Nikša Drinkovic, Department of Cardiovascular Diseases, University Hospital Centre Rebro, Kišpatićeva 12, 41000 Zagreb, Yugoslavia.

Br Heart J 1987;**58**:85–6

Correspondence

Transluminal angioplasty of a stenosis of an internal mammary artery graft

Sir,
In a recent paper (1986;**56**:473–5) Crean *et al* reported successful dilatation of the anastomotic stricture of an internal mammary artery graft. They stated that "early and late stenoses develop with a similar aetiology to those in vein grafts". This is not the conclusion of the study they quote.[1] On page 255 of the cited article it says "Failure of mammary grafts, early or late, was so infrequent that determinants of stenosis or occlusion could not be identified".

We would also like to point out that several recent reports suggest that an early anastomotic stricture is not due to atherosclerosis but is a surgical complication of suture technique.[2-4]

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References

1 Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor BC. Long term serial studies of internal mammary artery and saphenous vein coronary bypass grafts. *J Thorac Cardiovasc Surg* 1985; **89**:248–58.
2 Kereiakes DJ, George B, Stertzer SH, Myler RK. Percutaneous transluminal angioplasty of left internal mammary grafts. *Am J Cardiol* 1985;**55**:1215–6.
3 Zaidi AR, Hollman JL. Percutaneous angioplasty of internal mammary artery graft stenosis: case report and discussion. *Cathet Cardiovasc Diagn* 1985;**11**: 603–8.
4 Steffenino G, Meier B, Finci L, von Segesser L, Velebit V. Percutaneous transluminal angioplasty of right and left internal mammary artery grafts. *Chest* 1986;**6**:849–51.

Long term improvement in global left ventricular function after early thrombolytic treatment in acute myocardial infarction

Sir,
We were interested to read the report of long term improvement in global left ventricular function after early thrombolytic treatment in acute myocardial infarction by Res *et al* (1986;**56**:414–21). They noted that the improvement in left ventricular ejection fraction (9%) after thrombolysis was greater in patients who had sustained an anterior infarction than in those with inferior infarctions. They claimed then this was due to photon attenuation. Because this difference between anterior and inferior infarction has been reported by other groups including ourselves[1] it is worth examining the question of photon attenuation more closely.

Res *et al* used the theoretical calculations of Yeh and Yeh[2] as a basis for their statement; however Yeh and Yeh examined why the ejection fraction measured by radioisotope methods gave a lower value than that measured by contrast ventriculography. The larger the heart the greater the photon attenuation and events in the posterior wall are subject to greater attenuation than events in the anterior wall. Nevertheless, the overall effect on the calculation of ejection fraction was small ($<5\%$) and Yeh and Yeh did not assess the influence of abnormal wall movement.

Schneider *et al* examined the effects of regional hypokinesis in heart model studies. They concluded that with anterior hypokinesis the ejection fraction was underestimated but with posterior hypokinesis ejection fraction was overestimated.[3] They suggested that the effects of regional hypokinesis on ejection fraction could be corrected by considering differential count attentuation but they cautioned that their heart model was a worst case example, since anterior and inferior hypokinesis do not occur in a strict anterior or posterior projection. In the heart model the effects were greatest when left ventricular volume was large and ejection fraction was low. This would not be the case in inferior infarction.

Knowledge of data from contrast ventriculography[4] means that Res *et al* could examine this point more precisely by presenting the correlation between the contrast and radionuclide ventriculograms.

Res *et al* raise an important issue and their explanation may indeed be correct. The radionuclide method may fail to measure an improvement in ventricular function after streptokinase treatment if successful treatment reduces posterior wall hypokinesis resulting in a smaller overestimation of ejection fraction. There are important implications for other studies that use radionuclide data and this hypothesis deserves close examination.

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References

1 Been M, de Bono DP, Muir AL, Boulton FE, Hillis WS, Hornung R. Coronary thrombolysis with intravenous anisoylated plasminogen-streptokinase complex BRL 26921. *Br Heart J* 1985;**53**:253–9.
2 Yeh EL, Yeh YS. Theoretical errors in radionuclide ejection fraction study due to photon attenuation. *Eur J Nucl Med* 1981;**6**:69–71.
3 Schneider RM, Jaszczak RJ, Coleman RE, Cobb FR. Disproportionate effects of regional hypokinesis on regional ejection fraction: compensation using attenuation-corrected ventricular volumes. *J Nucl Med* 1984;**25**:747–54.
4 Serruys PW, Simoons ML, Suryapranata H, *et al.* Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 1986;**7**:729–42.

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The Heart and Stroke

Exploring Mutual Cerebrovascular and Cardiovascular Issues
Editor: A. J. Furlan, Cleveland
1987. Approx. 410 pages. (Clinical Medicine and the Nervous System). Hard cover DM 110,–. ISBN 3-540-16206-2

The book offers extensive coverage of cardioembolic stroke, including a brand new contribution on the mechanism of hemorrhagic infarction. Controversial topics such as anticoagulation, combined carotid and coronary surgery and screening for silent coronary disease are covered.

Atherogenesis and Aging

Editors: S. R. Bates, Philadelphia; **E. C. Gangloff,** Bethesda
1987. 86 figures. XV, 213 pages. Hard cover DM 148,–
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Atherogenesis and Aging explores the relationship between atherosclerosis development and the aging process, in particular those intrinsic aging-related physiologic changes which may precipitate or accelerate atherogenesis. Such changes include marked alterations in immune response capacity, hormone regulation, and aortic ultrastructure, as well as enhanced glycosylation of collagen and lens crystallin.

G. Stehle, R. Bernhardt, Heidelberg

Coronary Risk Factors in Japan and China

(Sitzungsberichte der Heidelberger Akademie der Wissenschaften, Mathematisch-naturwissenschaftliche Klasse, Jahrgang 1987)
1987. 23 figures, 22 tables. IX, 53 pages. Soft cover DM 34,–
ISBN 3-540-17392-7

Contents: Blood Lipid Patterns in 13630 Healthy Japanese. – Coronary Risk Factors in China: A Comparative Study on Middle-aged Workers between China and Germany.

Neural Mechanisms and Cardiovascular Disease

Proceedings of the International Symposium held in S. Margherita Ligure, Italy, in May 1985
Editors: A. Malliani, Milan; **B. Lown,** Cambridge, MA; **M. Prosdocimi,** Abano Terme
FIDIA Research Series
1986. Approx. 650 pages. Hard cover DM 220,–
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G. Schlag, H. Redl, Vienna (Eds.)

Volume 5

Thoracic Surgery – Cardiovascular Surgery

1986. XVIII, 218 pages. (Fibrin Sealant in Operative Medicine, Volume 5). Soft cover DM 56,–. ISBN 3-540-17141-X

J. Møller, Copenhagen

Cholesterol

Interactions with Testosterone and Cortisol in Cardiovascular Diseases

With a foreword by H. Einfeldt

1987. 4 figures, 12 color photographs. X, 76 pages. Hard cover DM 68,– ISBN 3-540-17097-9

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H. Just, Freiburg; **P. H. Heintzen,** Kiel (Eds.)

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H. Kurosawa, Tokyo, **A. E. Becker,** Amsterdam

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F. Unger, Salzburg (Ed.)

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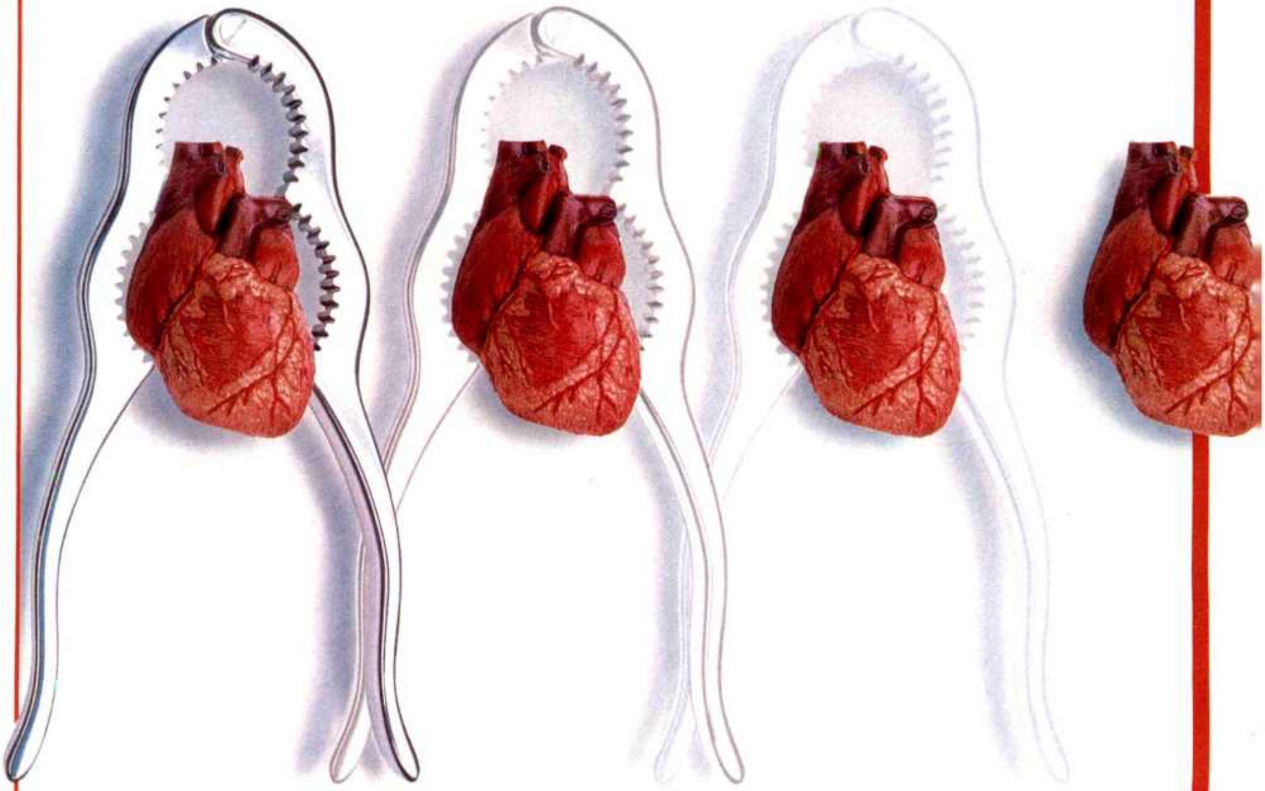

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Br Heart J 1987;58:87–8

Editorial

Uncertainties about interpretation of ventricular stimulation studies in patients with Wolff-Parkinson-White syndrome

KILLIAN ROBINSON, DENNIS M KRIKLER

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Arrhythmia is common and important in the Wolff-Parkinson-White syndrome, and indeed many would agree that both pre-excitation *and* supraventricular arrhythmia are essential features of the classical expression of this syndrome. Reentrant atrioventricular tachycardia is the most commonly encountered arrhythmia in the syndrome, but atrial fibrillation and to a lesser extent flutter are seen in 10–32% of patients.[1] Independent, coincidental arrhythmias, such as intranodal reciprocating tachycardia, are unusual.[2] There is of course the fear of ventricular fibrillation[3 4]; and a small risk of sudden death has been reported.[3–5]

In this issue of the *British Heart Journal* (p. 89), Brembilla-Perrot and her colleagues examine the occurrence of ventricular tachycardia in the Wolff-Parkinson-White syndrome. They compared the electrophysiological findings in 46 patients with pre-excitation with those in 36 controls in whom there was no evidence of pre-excitation. Programmed stimulation induced ventricular tachycardia in 37% of patients with pre-excitation and in 3% of the controls. The problem in the Wolff-Parkinson-White syndrome is not, however, ventricular tachycardia but rather ventricular fibrillation.

Clinically significant spontaneous ventricular tachycardia is rare in the pre-excitation syndrome: only one case was noted in each of two series of 139 and 163 patients[6 7]: and another review of reported cases of pre-excitation also found that this arrhythmia was uncommon.[8] When spontaneous ventricular tachycardia occurs it seems to be associated with underlying heart disease.[9] Furthermore, when ventricular fibrillation complicates the Wolff-Parkinson-White syndrome it is usually preceded by atrial fibrillation and not by ventricular tachycardia. Non-sustained multiform ventricular tachycardia is often observed at electrophysiological study and may be induced in normal individuals if the stimulation protocol is sufficiently aggressive.[10] With the protocol used in the current study, and in that of Milstein *et al*,[11] however, the expected frequency of induced ventricular tachycardia would be low, perhaps 0·7%[12] or 3%.[13]

Nevertheless, there are now two studies, the present one and that of Milstein *et al*,[11] which show that inducible ventricular tachycardia is more common in patients with the Wolff-Parkinson-White syndrome than in control groups. The question whether this feature is a further non-specific, but sensitive, indicator of the risk of ventricular fibrillation will only be resolved by long term follow up and knowledge of other possible risk factors, such as a history of both reciprocating tachycardia and atrial fibrillation with short maximally pre-excited RR intervals.[4] On its own, however, the importance of inducible ventricular tachycardia is doubtful because the frequency of sudden death in the pre-excitation syndrome is not even remotely near 37%: in clinical experience it is rare, and it was not encountered in one review.[14]

How do these findings affect the management of patients with the Wolff-Parkinson-White syndrome? The answer is hardly at all. From a clinical standpoint, decisions will continue to be based either on symptoms or on the presumed risk of ventricular fibrillation as assessed by the anterograde conduction properties of the accessory pathway.[15] From the epidemiological point of view, as various forms of treatment, including surgical ablation of

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the accessory pathway, reduce the number of patients with the Wolff-Parkinson-White syndrome considered to be at high risk, it will become impossible to evaluate any dangers of susceptibility to inducible ventricular tachycardia and its relation to other high risk factors for sudden death. This may be for the best as, whatever the shortcomings of assessing risk from the conduction properties of the accessory pathway, there will be endless problems, both medical and socioeconomic, if too much weight is placed on non-specific ventricular responses to programmed stimulation. Indeed, in a recently published consensus statement there was no agreement about the value of programmed stimulation in the identification of ventricular tachycardia (save in specific circumstances), and in the Wolff-Parkinson-White syndrome it was proposed that very rigid criteria, including drug-refractory arrhythmia, must be fulfilled before routine study is warranted.[16] Longevity in the Wolff-Parkinson-White syndrome is by no means rare[17] and one should be very careful before deducing high risk from the results of invasive studies, in the face of clinical experience.

This having been said, the results presented by Brembilla-Perrot and her colleagues will be studied with interest and taken into account by those performing electrophysiological studies in patients with the Wolff-Parkinson-White syndrome. It should not take long to assess whether ventricular stimulation of this sort is relevant to the Wolff-Parkinson-White syndrome; this will give us more confidence in the management of our patients with this syndrome. If the clinical relevance of what Brembilla-Perrot *et al* say turns out to be highly limited, it will provide further reassurance about the management of the vast majority of patients with this disorder.

References

1 Campbell RWF, Smith RA, Gallagher JJ, Pritchett ELC, Wallace AG. Atrial fibrillation in the pre-excitation syndrome. *Am J Cardiol* 1977; **40**:514–20.

2 Spurrell RAJ, Krikler D, Sowton E. Two or more intra AV nodal pathways in association with either a James or Kent extranodal bypass in 3 patients with paroxysmal supraventricular tachycardia. *Br Heart J* 1973;**35**:113–22.

3 Dreifus LS, Haïat R, Watanabe Y, Arriaga J, Reitman N. Ventricular fibrillation: a possible mechanism of sudden death in patients with the Wolff-Parkinson-White syndrome. *Circulation* 1971;**43**:520–7.

4 Klein GJ, Bashore TM, Sellers TD, Prichett ELC, Smith WM, Gallagher JJ. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *N Engl J Med* 1979;**301**:1080–5.

5 Brembilla-Perrot B, Aliot E, Louis P, *et al*. Devenir de 195 patients atteints de syndrome de Wolff-Parkinson-White. *Arch Mal Coeur* 1987; **80**:271–7.

6 Wellens HJJ. The electrophysiological properties of the accessory pathway in the Wolff-Parkinson-White syndrome. In: Wellens HJJ, Lie KI, Janse MJ, eds. *The conduction system of the heart*. Philadelphia: Lea and Febiger, 1976:567–87.

7 Benditt DG, Pritchett ELC, Gallagher JJ. Spectrum of regular tachycardia with wide QRS complexes in patients with accessory atrioventricular pathways. *Am J Cardiol* 1978;**42**:828–38.

8 Reddy CP, Sartini JC, Kuo CS. Paroxysmal ventricular tachycardia in Wolff-Parkinson-White syndrome: case report and review of the literature. *J Electrocardiol* 1982;**15**:403–10.

9 Krikler DM, Davies MJ, Rowland E, Goodwin JF, Evans RC, Shaw DB. Sudden death in hypertrophic cardiomyopathy: associated accessory atrioventricular pathways. *Br Heart J* 1980;**43**:245–51.

10 Brugada P, Green M, Abdolleh H, Wellens HJJ. Significance of ventricular arrhythmias initiated by programmed ventricular stimulation: the importance of the type of ventricular arrhythmias induced and the number of premature stimuli required. *Circulation* 1984;**69**:87–92.

11 Milstein S, Sharma AD, Klein GJ. Non clinical ventricular tachycardia in the Wolff-Parkinson-White syndrome. *PACE* 1985;**8**:178–83.

12 Vandepol CJ, Farshidi A, Spielman SR, Greenspan AM, Horowitz LN, Josephson ME. Incidence and clinical significance of induced ventricular tachycardia. *Am J Cardiol* 1980;**45**: 725–31.

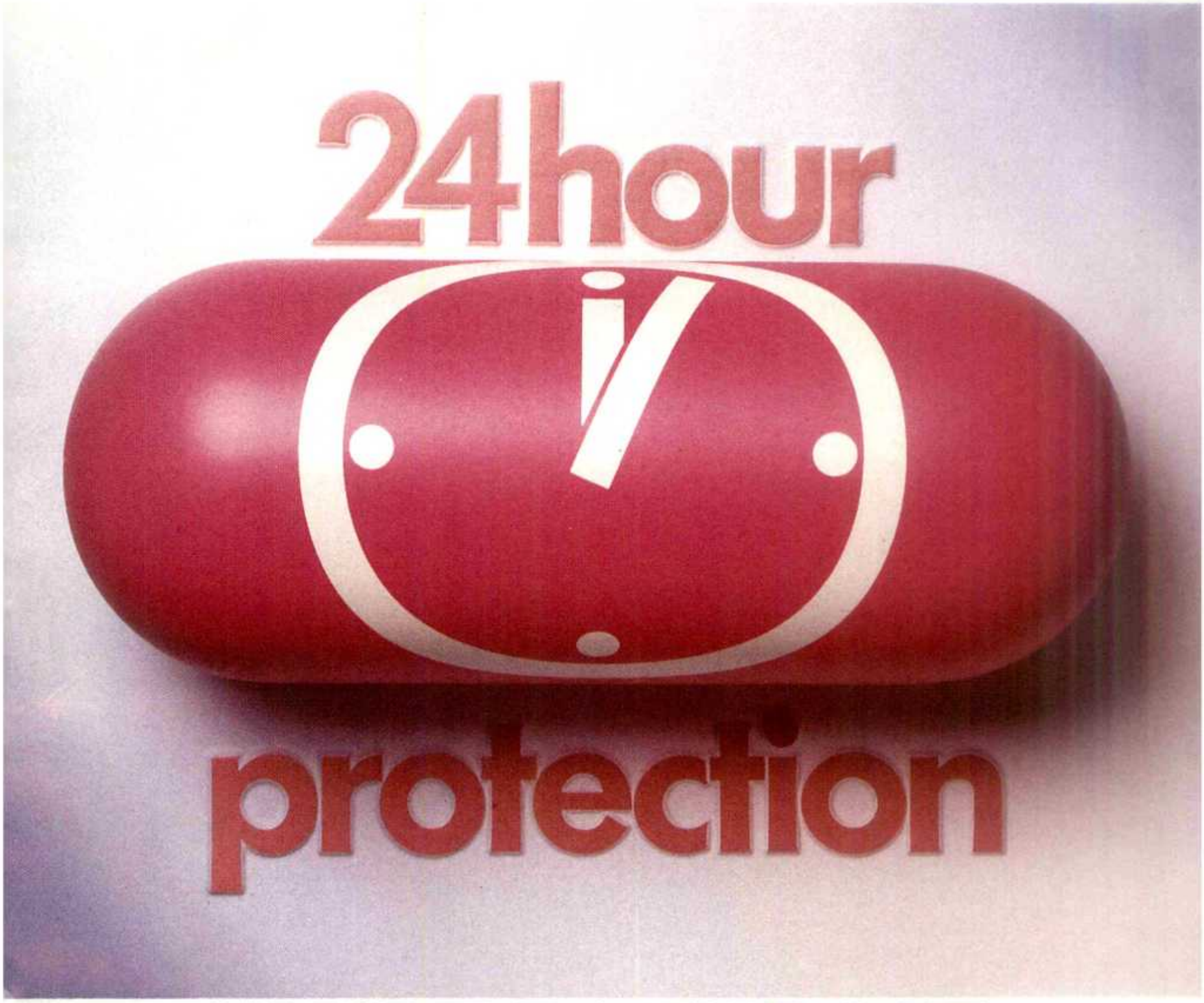
13 Livelli FD, Bigger JT, Reiffel JA, *et al*. Response to programmed ventricular stimulation: sensitivity, specificity and relation to heart disease. *Am J Cardiol* 1982;**50**:452–8.

14 Krikler DM. The Wolff-Parkinson-White and related syndromes. In: Krikler DM, Goodwin JF, eds. *Cardiac arrhythmias, the modern electrophysiological approach*. London: WB Saunders, 1975:144–81.

15 Rowland E, Curry P, Fox K, Krikler D. Relation between atrioventricular pathways and ventricular response during atrial fibrillation and flutter. *Br Heart J* 1981;**45**:83–7.

16 Rahimtoola SH, Zipes DP, Akhtar M, *et al*. Consensus statement of the conference on the state-of-the art of electrophysiologic testing in the diagnosis and treatment of patients with cardiac arrhythmias. *Circulation* 1987;**75**(suppl III):3–11.

17 Krikler DM. Wolff-Parkinson-White syndrome: long follow-up and an Anglo-American historical note. *J Am Coll Cardiol* 1983;**2**:1216–8.



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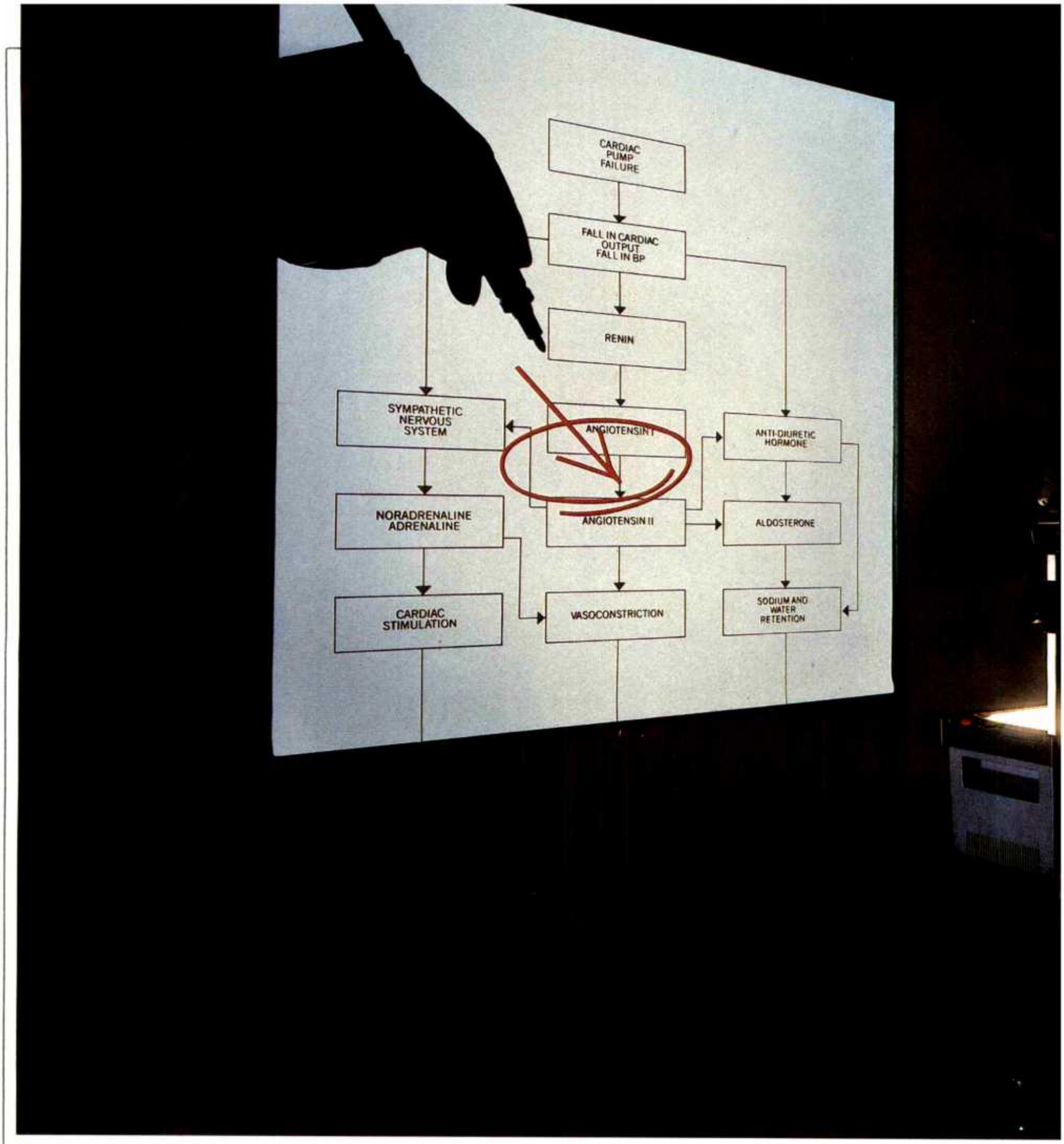

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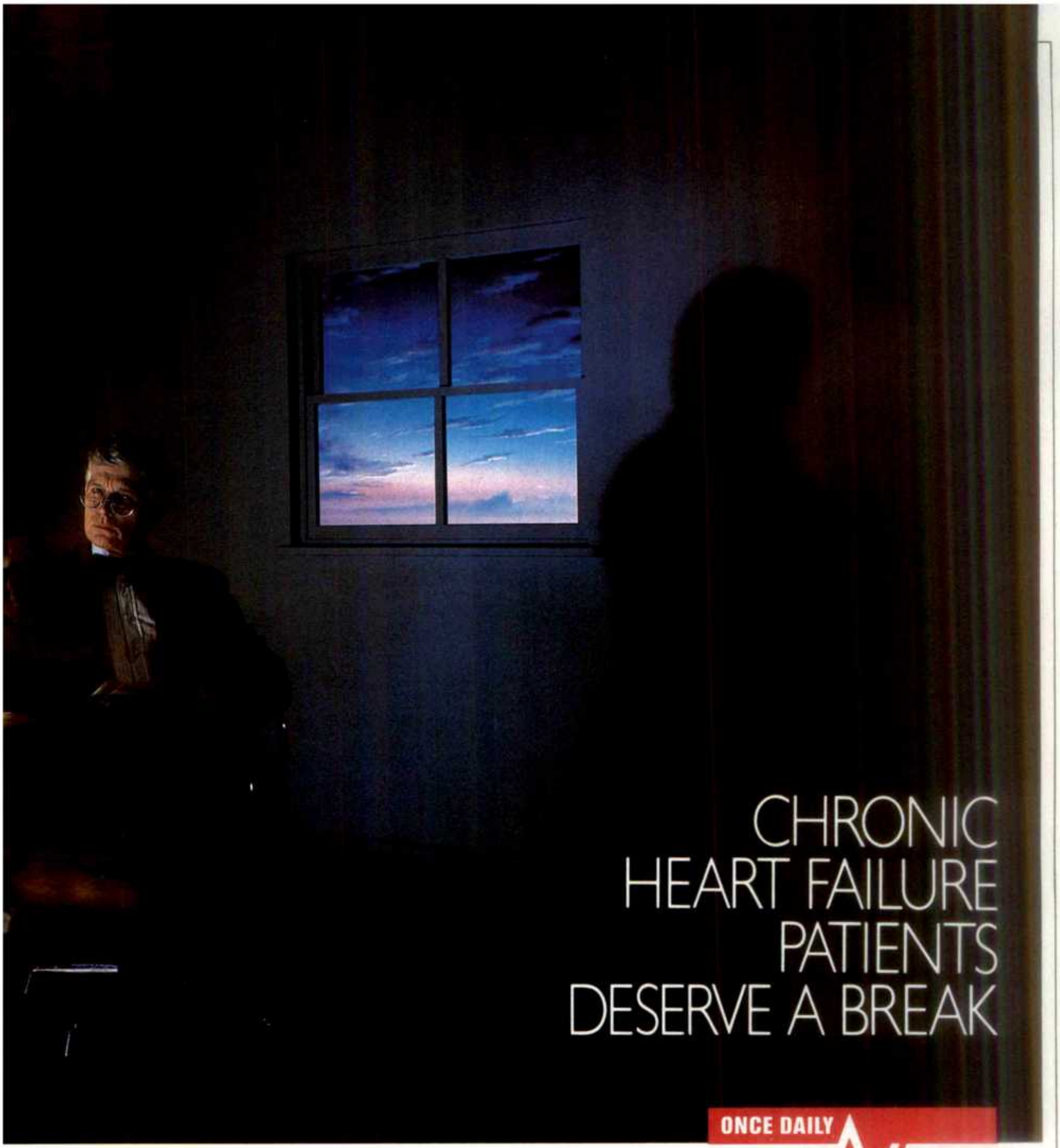

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Full prescribing information is available and should be consulted before prescribing.

USES

All grades of essential hypertension and renovascular hypertension where standard therapy is ineffective or inappropriate because of adverse effects.

In congestive heart failure, as adjunctive therapy with digitalis and diuretics, treatment should always be initiated in hospital.

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Essential and renovascular hypertension: Therapy should be initiated with 5 mg in patients under 65 years of age; 2.5 mg if older or in presence of renal impairment. The usual maintenance dose is 10–20 mg once daily; maximum 40 mg once daily. When adding to a diuretic, the starting dose of 'Innovace' is 2.5 mg with the diuretic discontinued for 2–3 days prior to 'Innovace', if possible.

Reduce beta-blocker dose gradually after starting 'Innovace'. Dose titrate to BP requirements. Dosage of other antihypertensives may need adjusting.

Congestive heart failure: Can be used as adjunctive therapy with diuretics and, where appropriate, digitalis. Initial daily dose 2.5 mg under close supervision in hospital. If possible, diuretic dose should be reduced beforehand. Monitor blood pressure closely for hypotension.

Increase dose gradually to usual maintenance dose of 10–20 mg daily.

MODE OF ACTION

Following oral administration, 'Innovace' is rapidly absorbed and hydrolysed to enalaprilat, a highly specific, long-acting, non-sulphydryl angiotensin-converting enzyme inhibitor.

CONTRA-INDICATIONS

Pregnancy: assessment for possible pregnancy required if menstrual period is missed. Hypersensitivity.

PRECAUTIONS

Assess renal function prior to therapy with 'Innovace' and during treatment where appropriate. Should not be given with aortic stenosis or outflow tract obstruction.

Symptomatic hypotension is more likely following volume depletion caused by diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting or in patients with congestive heart failure with or without renal insufficiency. Severe hypotension reported mainly in patients with severe heart failure.

Impaired renal function: Caution should be used in patients with renal impairment. Renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Renal failure has been reported, mainly in patients with severe congestive heart failure or underlying renal disease, and is usually reversible. Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying artery stenosis. 'Innovace' is dialysable.

Renovascular hypertension: 'Innovace' can be used when surgery is not indicated or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases in blood urea and creatinine, reversible upon discontinuation of therapy, have been seen.

Because it is not known whether 'Innovace' is excreted in human milk, caution required if given to nursing mothers. Has not been studied in children.

Surgery/anaesthesia: 'Innovace' may lead to hypotension requiring volume expansion.

Drug interactions: Increased antihypertensive effect when combined with methyldopa, beta-blockers, calcium antagonists, or diuretics. Adrenergic-blocking drugs should be added with caution. Concomitant propranolol may reduce bioavailability. Lithium levels may be increased.

Plasma potassium usually remains within normal limits. 'Innovace' may elevate plasma potassium levels in patients with renal failure. Potassium supplements or potassium-sparing diuretics are not usually recommended, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. If deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

SIDE EFFECTS

Severe hypotension and renal failure.

Angioneurotic oedema has occurred rarely. Discontinue 'Innovace'; condition usually resolves without treatment, but give subcutaneous adrenaline (0.5 ml 1:1,000) if airways obstruction likely.

Most frequently, dizziness, and headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, urticaria, dysgeusia, and cough.

Clinical laboratory findings: Increased blood urea and plasma creatinine, decreases in haemoglobin, platelets, white cell count, and elevation of liver enzymes have occurred in a few patients, but causal relationship not established.

Overdosage: Hypotension most likely manifestation.

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Tablets 20 mg: calendar packs of 28 tablets, £13.10; bottles of 50 tablets, £23.40. Tablets 10 mg: calendar packs of 28 tablets, £11.03; bottles of 50 tablets, £19.69. Tablets 5 mg: calendar packs of 28 tablets, £7.86; bottles of 50 tablets, £14.03. Tablets 2.5 mg: Bottles of 50 tablets, £10.

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Inducible multiform ventricular tachycardia in Wolff-Parkinson-White syndrome

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SUMMARY The induction of ventricular tachycardia by ventricular stimulation was investigated in 46 patients with isolated Wolff-Parkinson-White syndrome (10 concealed) and 36 control patients with normal electrocardiograms and conduction systems. None of those studied had spontaneous ventricular arrhythmias or myocardial or valve disease. Single and double ventricular extrastimuli were delivered at 3 cycle lengths (sinus, 600 ms, 400 ms). In the controls ventricular simulation induced one episode (3%) of non-sustained ventricular tachycardia. Ventricular stimulation in patients with Wolff-Parkinson-White syndrome induced two episodes of ventricular fibrillation and 15 episodes of non-sustained multiform ventricular tachycardia (37%). Ventricular arrhythmias were induced only in patients with overt Wolff-Parkinson-White syndrome. In 14 patients the conformation of the electrocardiogram at the start of ventricular tachycardia resembled that of major pre-excitation. The absence of inducible ventricular tachycardia in patients with concealed Wolff-Parkinson-White syndrome suggests that anterograde conduction via an atrioventricular accessory pathway is required to initiate the ventricular arrhythmias: the ventricular tachycardia may be associated with reentry of impulses via atrioventricular connection during the phase of ventricular vulnerability. The similarity between the start of ventricular tachycardia and pre-excitatory complexes may also indicate local reentry into the ventricular area occupied by the bypass tracts.

Patients with Wolff-Parkinson-White syndrome and anterograde pre-excitation are more likely to have inducible multiform ventricular tachycardia than individuals without Wolff-Parkinson-White syndrome.

Patients with Wolff-Parkinson-White syndrome may present with syncope which is often assumed to be related to atrial fibrillation with a rapid ventricular response caused by conduction through an atrioventricular connection. Ventricular tachycardia has also been regarded as the probable cause of neurological symptoms in patients with ventricular pre-excitation.[1]

We have compared the occurrence of ventricular tachycardia induced by programmed electrical stimulation in patients with Wolff-Parkinson-White syndrome with that in control patients.

Patients and methods

PATIENTS

We studied 46 patients with the Wolff-Parkinson-White syndrome (28 men and 18 women, aged 8 to 62 years (36 (14))). Wolff-Parkinson-White syndrome was diagnosed in 36 patients who had the typical delta wave recorded in electrocardiograms taken during sinus rhythm. Ten patients had an accessory pathway that conducted only in the retrograde direction. Electrophysiological studies were performed to measure the effective refractory period of the bypass tracts or the mechanism of paroxysmal junctional tachycardia. Twenty four hour Holter monitoring and exercise test had established the absence of spontaneous ventricular arrhythmias. No evidence of ischaemic, myocardial, valvar, hyper-

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tensive, or congenital heart disease was found in any of the patients by examination, chest *x* ray, cross sectional echocardiography, or coronary angiography (in men who were $\geqslant 50$). Seventeen patients presented with dizziness or syncope.

We also studied 36 control patients (20 men and 16 women, aged 18 to 80 years (47(17))). None of the controls had Wolff-Parkinson-White syndrome or ventricular arrhythmias on Holter monitoring. The case history, physical examination, chest *x* ray, electrocardiogram, echocardiography, and electrophysiological study established that none of the control patients had underlying heart disease. Eleven control patients had an electrophysiological examination to investigate the cause of syncope which was later found to be related to a non-cardiac cause, and 25 had it to evaluate paroxysmal sinus bradycardia or first degree atrioventricular block which were reversed by atropine.

ELECTROPHYSIOLOGICAL TESTING

All patients were studied in the non-sedated post-absorptive state after they had given their informed consent. The right heart was catheterised via the femoral vein with three 6 or 7 French multi-electrode catheters. Electrograms were routinely recorded from the right atrium, atrioventricular junction (His bundle electrogram), and distal coronary sinus. Surface electrocardiographic leads I, III, V1, V6, and intracardiac electrograms were recorded at paper speed of 25 and 100 mm/s on a Siemens multi-channel oscilloscopic recorder. Pacing stimuli were given by a programmable stimulator (Medtronic 1325) for 1·8 s at a strength that was approximately twice the diastolic threshold. The following electrophysiological variables were measured during the study:

(a) AH and HV basic intervals.

(b) Anterograde atrioventricular conduction, assessed by atrial pacing at incremental rates until second degree atrioventricular block occurred.

(c) The refractory periods of the anterograde conduction system determined by extrastimuli techniques; premature atrial stimulation (A/2) was introduced during sinus rhythm and during driven atrial rhythm at a cycle length of 600 ms.

(d) Retrograde ventricular atrial conduction assessed by ventricular pacing at an incremental rate up to 200 beats/min.

(e) In patients with Wolff-Parkinson-White syndrome in whom atrial fibrillation had not been induced by any of the preceding procedures rapid atrial pacing was performed until atrial fibrillation was induced.

(f) Programmed ventricular stimulation was given at the apex and, in some patients, at the infundibulum of the right ventricle. It was performed as follows: single premature ventricular extrastimulus (S2) was introduced in late diastole during sinus rhythm and paced cycle lengths (S1–S2 intervals of 600 and 400 ms) and the interval was shortened until the ventricle became refractory. Double ventricular extrastimuli (S2 and S3) were introduced during sinus rhythm and during paced cycle lengths starting with an S1–S2 interval that was 10–20 ms longer than the ventricular refractory period; the S2–S3 interval was shortened until S3 did not depolarise the ventricles.

The reproducibility of the initiation of ventricular tachycardia (except for induced ventricular fibrillation) was assessed by performing the stimulation on three occasions after an interval of a few minutes.

DEFINITIONS

The following definitions were used:

Sustained ventricular tachycardia—This lasted for more than 1 minute or required termination by programmed ventricular stimulation or cardioversion before that time.

Non-sustained ventricular tachycardia—A run of at least five consecutive ventricular complexes which terminated spontaneously in <60 s.

Multiform ventricular tachycardia—Ventricular tachycardia with an unstable (continuously varying) QRS complex configuration recorded in any electrocardiographic lead.

Repetitive ventricular response—One to four intraventricular reentries.

Concealed accessory atrioventricular connection was diagnosed during reciprocating tachycardia if one of the following criteria was satisfied:

(a) Demonstration of eccentric activation by endocardial catheter mapping.

(b) If premature ventricular depolarisation during reciprocating tachycardia when the bundle of His was refractory caused pre-excitation of the atrium.

Results

RESPONSES TO PROGRAMMED VENTRICULAR STIMULATION

Ventricular tachycardia was induced in 17 (37%) of the 46 patients with Wolff-Parkinson-White syndrome and in only one of the 36 control patients without Wolff-Parkinson-White syndrome. In patients with Wolff-Parkinson-White syndrome all the ventricular tachycardias were multiform, rapid (cycle length 150 to 200 ms), and they could be reproduced by repeat testing. The diagnosis of ventricular tachycardia was based on the absence of His bundle deflection preceding the complexes of ventricular tachycardia and the existence of complete atrioventricular dissociation during ventricular tachycardia in all patients (fig).

Fifteen ventricular tachycardias were non-sustained. Two were ventricular fibrillation and required cardioversion to stop them. Ventricular arrhythmia was induced in 15 patients by the introduction of two ventricular extrastimuli during paced cycle length and in two patients by the introduction of two ventricular extrastimuli during sinus rhythm. The configuration of the beginning of ventricular tachycardia was similar to major ventricular pre-excitation in 14 patients (fig); this similarity was noted for the first, the second, or the third complex. All these ventricular arrhythmias were induced in patients with overt Wolff-Parkinson-White syndrome; ventricular tachycardia was not induced in patients with a concealed accessory pathway.

In the control group, only one episode of non-sustained, multiform ventricular tachycardia was induced by the S1, S2, S3 technique.

Intraventricular reentry was induced in 21 patients with Wolff-Parkinson-White syndrome and in 20 control patients.

CORRELATIONS BETWEEN CLINICAL AND ELECTROPHYSIOLOGICAL FINDINGS AND INDUCIBILITY OF MULTIFORM VENTRICULAR TACHYCARDIA IN PATIENTS WITH THE WOLFF-PARKINSON-WHITE SYNDROME

Tables 1 and 2 summarise the results. The 17 patients who had inducible ventricular tachycardia were not statistically different in terms of age (31 (14) *vs* 38 (14)), sex, or location of the atrioventricular connection from the 29 patients in whom ventricular arrhythmia was not induced (table 2).

The occurrence of dizziness or syncope was similar in both groups. In the ten patients with syncope and without inducible ventricular tachycardia, however, syncope could be explained by a short refractory period in the Kent bundle in three patients, carotid sinus hypersensitivity in four patients, and associated conduction disturbances in two patients. One patient had unexplained syncope. In the seven patients with syncope and inducible ventricular tachycardia, three had syncope associated with a short Kent bundle refractory period and in four the cause of the syncope was not known.

The occurrence of atrial fibrillation or flutter was not statistically different in the two groups; however, atrial fibrillation was more common in patients with inducible ventricular tachycardia (5/17 (29%))

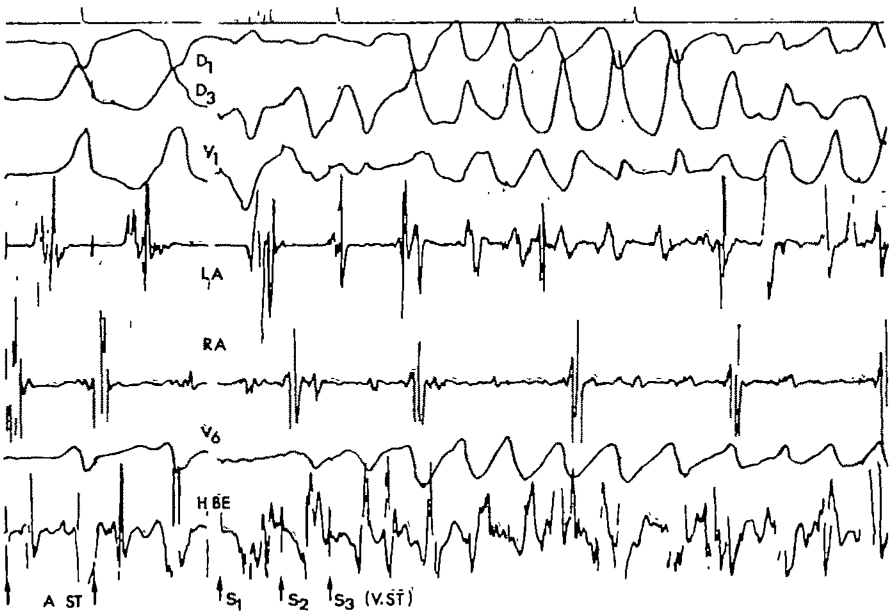

Figure *Electrocardiogram obtained during programmed ventricular stimulation in a patient (case 10) with type A Wolff-Parkinson-White syndrome. One atrial premature extrastimulus (left) caused a major pre-excitation complex. Ventricular extrastimuli (S1, S2, S3) induced a multiform ventricular tachycardia which degenerated into ventricular fibrillation (panel 2); the first complexes resemble those of pre-excitation complexes A ST, atrial stimulation; V ST, ventricular stimulation; H BE, His bundle electrogram; RA, right atrium; LA, left atrium; D1, V1; D3, V6.*

Table 1 *Data on patients and their electrophysiological characteristics*

Patient	*Age (yr)*	*Symptoms*	*Location of pathway*	*Anterograde ERP of AP at PCL (600 ms)*	*Shortest R-R during atrial fibrillation (ms)*	*Shortest PCL with 1:1 retrograde conduction (ms)*	*Induced SV arrhythmia*	*Induced ventricular arrhythmia and number of ventricular reentries*
1	25	D–T	S	280	375	430	AF	NS VT (17)
2	36	S	L	450	375	350	AF	NS VT (12)
3	29	T	L	250	260	<300	PJT–AF	NS VT (7)
4	59	S–T	S	350	750	315	PJT	NS VT (16)
5	32	T	R	230	350	<300	PJT	NS VT (11)
6	22	T	L	500	> 600	<300	PJT	NS VT (7)
7	42	T	S	290	545	<300	PJT	NS VT (5)
8	15	S–T	S	210	170	<300	PJT–AF	NS VT (11)
9	56	T	L	240	250	<300	PJT	VF
10	15	D–T	L	230	330	<300	PJT	VF
11	8	0	R	230	230	<300	PJT	NS VT (62)
12	15	D	S	330	545	<300	PJT	NS VT (6)
13	34	0	S	350	315	350	PJT	NS VT (11)
14	39	D	S	220	220	<300	PJT–AF	NS VT (7)
15	25	T	L	330	250	<300	PJT–AF	NS VT (6)
16	32	T	L	240	200	<300	PJT–AF	NS VT (14)
17	47	T	L	280	>600	<300	PJT	NS VT (37)
18	21	T	R	230	210	<300	PJT–AF	—
19	31	0	R + S	300	375	350	PJT	—
20	40	0	R	380	285	400	PJT	3
21	50	T	L	340	400	300	PJT	1
22	27	T	L	200	180	<300	PJT–AF	3
23	24	T	L	400	1000	<300	PJT	3
24	37	0	S	300	400	600	—	2
25	40	D	S	180	250	<300	PJT	—
26	57	S–T	L	600	1000	300	PJT	1
27	33	S	S	450	375	330	—	—
28	33	S	L	600	1000	375	PJT	3
29	55	S–T	L	210	250	<300	PJT	—
30	35	0	S	400	1000	460	—	—
31	15	0	S	200	300	<300	—	—
32	39	0	S	250	260	<300	PJT–AF	3
33	25	S–T	S	240	270	400	AF	3
34	67	S–T	L	310	285	<300	PJT	1
35	22	T	L	500	600	<300	PJT	2
36	25	S	S	550	1000	375	—	—
37	29	T	L	Concealed	—	330	PJT	1
38	29	T	L	Concealed	—	430	PJT	3
39	54	T	L	Concealed	—	330	PJT	3
40	62	D–T	L	Concealed	—	315	PJT–AF	1
41	39	T	L	Concealed	—	<300	PJT	2
42	58	T	L	Concealed	—	330	PJT	0
43	37	T	L	Concealed	—	460	PJT	1
44	28	D–T	S	Concealed	—	<300	PJT	2
45	47	T	S	Concealed	—	333	PJT	2
46	32	T	L	Concealed	—	300	PJT	2

Symptoms· D, dizziness, S, syncope; T, tachycardia. Location of pathway: L, left lateral; R, right lateral; S, septal. Anterograde ERP of AP at PCL: AP, accessory pathway; ERP, effective refractory period; PCL, paced cycle length. Induced SV arrhythmia: AF, atrial fibrillation or flutter; PJT, paroxysmal junctional tachycardia; SV, supraventricular Induced ventricular arrhythmia. NS, non-sustained, VF, ventricular fibrillation; VT, ventricular tachycardia.

than in patients without inducible ventricular tachycardia (5/29 (17%)). Only atrial fibrillation developing spontaneously during an induced episode of reciprocating tachycardia or during atrial pacing at an incremental rate of less than 200 beats/min was regarded as abnormal. The shortest paced cycle length associated with 1:1 retrograde conduction was significantly shorter in patients with inducible ventricular tachycardia (291 (45) *vs* 355 (125 ms)) ($p < 0.05$).

Ventricular arrhythmias were not induced in patients who had concealed accessory atrioventricular pathways that conducted only retrogradely.

In patients with overt Wolff-Parkinson-White syndrome, the anterograde refractory period of the accessory pathway(s) was short (<250 ms) in the basal state in seven (41%) patients with inducible ventricular tachycardia and in five (26%) without inducible ventricular tachycardia; the values of the

Table 2 *Characteristics of patients with Wolff-Parkinson-White syndrome with and without induced ventricular tachycardia (VT)*

Characteristics	*Patients with VT (17 patients)*	*Patients without VT (29 patients)*
Age (yr) (mean (SD))	31 (14)	38 (14)
Sex	12 M, 5 F	16 M, 13 F
Pathway location:		
Right	2	2
Left	8	16
Septal	7	10
Multiple	0	1
Associated atrial fibrillation	5	5
Syncope	7	10
Kent bundle refractory period:		
<250 ms	7	5
≥250 ms	10	14
Concealed		10

refractory periods of both subgroups were not significantly different (299 (83) *vs* 349 (137 ms)).

Three patients with induced non-sustained ventricular tachycardia who have been followed up for more than three years are free of ventricular arrhythmia.

Discussion

We found inducible multiform ventricular tachycardia in 37% of patients with Wolff-Parkinson-White syndrome and in 3% of controls. In patients with Wolff-Parkinson-White syndrome the ventricular arrhythmias were only induced in those with the overt syndrome.

Ventricular tachycardia is uncommon in patients with ventricular pre-excitation.[2,3] Although the occurrence of abnormally widened QRS complexes during paroxysmal arrhythmias in patients with accessory atrioventricular pathways has been noted in several reports, differentiation of ventricular tachycardia from supraventricular tachycardia with a wide QRS complex caused by ventricular pre-excitation can be difficult. The differential diagnosis is usually complex and only resolved by electrophysiological clinical study. In 26 patients with Wolff-Parkinson-White syndrome and a regular tachycardia with a wide QRS complex, Benditt *et al* found only one case of ventricular tachycardia.[4] A patient reported by Krikler *et al* who had concealed accessory bypass tracts died from ventricular fibrillation which complicated a ventricular tachycardia induced by atrial stimulation.[3] Lloyd *et al* considered the cause of the neurological symptoms in four patients with Wolff-Parkinson-White syndrome to be ventricular tachycardia.[1] This was because the electrophysiological characteristics of the accessory pathways were considered unlikely to support a tachycardia of a rate sufficient to result in syncope and programmed stimulation in the right ventricle induced non-sustained ventricular tachycardia. In the present study we found no correlation between syncope and induced multiform ventricular tachycardia, although ventricular tachycardia could explain the cause of neurological symptoms in four patients in whom the refractory period of the accessory pathway was long.

Milstein *et al* reported inducible multiform ventricular tachycardia in 10·1% of patients with Wolff-Parkinson-White syndrome .[5] The induction of this clinical ventricular tachycardia was not correlated with a specific electrophysiological finding. The patients were alive and well after a follow up of 20 (11) months.

The significance of induced ventricular tachycardias in patients without spontaneous ventricular arrhythmia is uncertain. Multiform ventricular tachycardia is the most frequent ventricular arrhythmia initiated by programmed electrical stimulation in patients without spontaneous sustained arrhythmias and without structural heart disease. The occurrence of this arrhythmia increases with the number of extrastimuli used in the stimulation protocol.[6] In most reports the occurrence of non-sustained ventricular tachycardia induced by two extrastimuli was low in normal subjects (0·7% to 2%).[7,8] In the study of Morady *et al* non-sustained ventricular tachycardia was not induced by stimulation with up to three extrastimuli in patients without structural disease who had no spontaneous ventricular tachycardia, but was frequently induced in patients with structural disease who had no spontaneous ventricular tachycardia.[9] None the less, a high frequency of multiform ventricular tachycardia was reported by Wellens *et al* in 32 patients without structural heart disease who were evaluated for suspected supraventricular arrhythmias; this arrhythmia was induced by up two extrastimuli during sinus rhythm and ventricular pacing in 38% of this group.[10]

In our study, non-sustained ventricular tachycardia was induced in only one (3%) of the control group. On the other hand, inducible non-sustained ventricular tachycardia was common (37%) in patients with Wolff-Parkinson-White syndrome and without other heart disease.

The high incidence of multiform ventricular tachycardia associated with the preexcitation syndrome resembles the high incidence of atrial fibrillation in Wolff-Parkinson-White syndrome (from 1% to 32%).[11] Atrial fibrillation in Wolff-Parkinson-White syndrome has been related[11-13] either to atrial reentry by an accessory pathway[13] or to a primary atrial vulnerability.[14] In the present study, ventricular tachycardia was not induced in patients who did not have anterograde conduction via accessory atrioventricular connection; and it may be that such a pathway is required to initiate ventricular tachycardia. Retrograde conduction to atria, which is present in all cases of Wolff-Parkinson-White syndrome, could be responsible for reentry of impulses through the atrioventricular connection and for the occurrence of ventricular depolarisation in the vulnerable phase. Hence atrial fibrillation in Wolff-Parkinson-White syndrome could lead to ventricular fibrillation.[15] In the present study only two patients had no retrograde conduction and ventricular tachycardia was not induced in them. Local reentry into the ventricular area containing the origin of the accessory pathway could also explain the similarity between the first QRS complexes of ventricular tachycardia and those of the pre-excitation QRS complex. All cases of pre-excitation with overt or concealed Wolff-Parkinson-White syndrome may be at high risk of inducible ventricular arrhythmias. This possibility could not be excluded because of the small number of patients with concealed Wolff-Parkinson-White syndrome. In the present study the appearance of the first premature ventricular contraction itself was related to ventricular stimulation. But there could have been automaticity in the accessory ventricular connection[16] or a ventricular premature complex caused by associated organic heart disease. Most spontaneous ventricular tachycardias in the Wolff-Parkinson-White syndrome are reported in patients with underlying heart disease, hypertrophic cardiomyopathy[1 3] or previous myocardial infarction.[1] Moreover, it has been shown that the prognosis of the Wolff-Parkinson-White syndrome is better in patients without associated organic heart disease.[17] In the present study, in a 56 year old patient with induced ventricular fibrillation, underlying heart disease was excluded by cross sectional echocardiography, right and left catheterisation, and coronary angiography. In a 15 year old boy who also presented with inducible ventricular fibrillation there was evidence of incipient hypertrophic cardiomyopathy on cross sectional echocardiography; however, this patient was a trained athlete. In the other patients with inducible non-sustained ventricular tachycardia, cross sectional echocardiograms were normal, but incipient associated right ventricular dysplasia could not be excluded. Two young women presenting a ballooning mitral valve without enlargement of left atrium and ventricle, did not have inducible ventricular tachycardia. No patient had protracted arrhythmias that could have caused a disorder indistinguishable from dilated cardiomyopathy.[18 19]

The worsening of prognosis when the Wolff-Parkinson-White syndrome is associated with another organic heart disease might be explained by mechanisms such as an increased atrial and ventricular vulnerability, leading to atrial fibrillation, followed by a ventricular fibrillation. Associated heart diseases are frequent in Wolff-Parkinson-White syndrome,[20 21] particularly ventricular diseases which could facilitate ventricular vulnerability, such as operated congenital heart disease, hypertrophic cardiomyopathy, or mitral valve prolapse.

Deaths related to Wolff-Parkinson-White syndrome are rare, however, and generally prognosis is considered to be good.[22] Eleven follow up studies of Wolff-Parkinson-White syndrome cases were published between 1962 and 1985. The incidence of deaths related to this syndrome ranged from 0 to 2%.[23] In a recent personal study, the follow up of 195 patients with Wolff-Parkinson-White syndrome for more than three years, there were only two deaths that could be related to this syndrome.[23] One of these was due to an atrial fibrillation, conducted through a Kent bundle with a short refractory period, and the other was a case of sudden death in a 12 year old girl during competitive sport. Neither a clinical examination nor a necropsy was performed in the latter case. There was a high frequency of associated heart disease (24%) and six deaths were related to a complex congenital heart disease.

Studies of the causes of deaths in the Wolff-Parkinson-White syndrome generally report that death was associated with atrial fibrillation with rapid ventricular response via the accessory pathway leading to ventricular fibrillation. The inducibility of ventricular tachycardia in a patient with Wolff-Parkinson-White syndrome therefore is probably not clinically important. Underlying heart disease, however, should always be sought. If it is found, the patient should be considered to be at risk of ventricular arrhythmias because electrical instability is being caused by the accessory pathway and by the associated heart disease.

We conclude that inducible multiform ventricular tachycardia is more common in patients with Wolff-Parkinson-White syndrome who have no organic heart disease but have anterograde pre-excitation than in patients without organic heart disease and without Wolff-Parkinson-White syndrome. Both advanced organic heart disease and the Wolff-Parkinson-White syndrome can lead to the induction of multiform ventricular tachycardia.

References

1 Lloyd EA, Hauer RN, Zipes DP, Heger JJ, Prystowsky

EN. Syncope and ventricular tachycardia in patients with ventricular preexcitation. *Am J Cardiol* 1983;52:79–82.

2 Reddy CP, Sartini JC, Kuo CS. Paroxysmal ventricular tachycardia in Wolff Parkinson White syndrome: case report and review of the literature. *J Electrocardiol* 1982;15:403–10.

3 Krikler DM, Davies MJ, Rowland E, Goodwin JF, Evans RC, Shaw DB. Sudden death in hypertrophic cardiomyopathy: associated accessory atrioventricular pathways. *Br Heart J* 1980;43:245–51.

4 Benditt DG, Pritchett ELC, Gallagher JJ. Spectrum of regular tachycardias with wide QRS complexes in patients with accessory pathways. *Am J Cardiol* 1978;42:828–38.

5 Milstein S, Sharma AD, Klein GJ. Non clinical ventricular tachycardia in the Wolff Parkinson White syndrome. *PACE* 1985;8:678–83.

6 Brugada P, Green M, Abdollah H, Wellens HJJ. Significance of ventricular arrhythmias initiated by programmed ventricular stimulation: the importance of the type of ventricular arrhythmia induced and the number of premature stimuli. *Circulation* 1984; 69:87–92.

7 Vandepol CJ, Farshidi A, Spielman SR, Greenspan AM, Horowitz LN, Josephson ME. Incidence and clinical significance of induced ventricular tachycardia. *Am J Cardiol* 1980;45:725–31.

8 Livelli FD, Bigger JT, Reiffel JA, *et al.* Response to programmed ventricular stimulation: sensitivity, specificity and relation to heart disease. *Am J Cardiol* 1982;50:452–8.

9 Morady F, Shapiro W, Shen E, Sung RJ, Scheinman MM. Programmed ventricular stimulation in patients without spontaneous ventricular tachycardia. *Am Heart J* 1984;107:875–82.

10 Wellens HJJ, Brugada P, Stevenson WG. Programmed electrical stimulation of the heart in patients with life threatening ventricular arrhythmias: what is the significance of induced arrhythmias and what is the correct stimulation protocol? *Circulation* 1985; 72:1–7.

11 Campbell RWF, Smith RA, Gallagher JJ, Pritchett EL, Wallace AG. Atrial fibrillation in the preexcitation syndrome. *Am J Cardiol* 1977;40:514–20.

12 Gressard A, Atallah G, Chatelain MT, Touboul P. Genèse de la fibrillation auriculaire dans le syndrome de Wolff-Parkinson-White. *Arch Mal Coeur* 1981; 74:1277–82.

13 Sung RJ, Castellanos A, Mallon SM, Bloom MG, Gelband H, Myerburg RJ. Mechanisms of spontaneous alternation between reciprocating tachycardia and atrial flutter—fibrillation in the Wolff Parkinson White syndrome. *Circulation* 1977;56:409–16.

14 Sharma AD, Klein GJ, Guiraudon GM, Milstein S. Atrial fibrillation in patients with Wolff Parkinson White syndrome. Incidence after surgical ablation of the accessory pathway. *Circulation* 1985;72:161–9.

15 Meijler FL, Van Der Tweel I, Herbschleb JN, Hauer RNW, Robles de Medina E. Role of atrial fibrillation and atrio-ventricular conduction including Wolff Parkinson White syndrome in sudden death. *J Am Coll Cardiol* 1985;5:17B–22B.

16 Leclercq JF, Cauchemez B, Attuel P, Childers R, Coumel Ph, Slama R. Rythme réciproque antidromique sur Wolff-Parkinson-White declenché par une extrasystolie ventriculaire provenant du lieu d'émergence de la voie de préexcitation. *Arch Mal Coeur* 1983;76:95–103.

17 Giardina ACV, Ehlers KH, Engle MA. Wolff-Parkinson-White syndrome in infants and children. A long-term follow-up study. *Br Heart J* 1972;34:839–46.

18 Warnowicz MA, Santucci B, Buchelerev G, Denes P. Myocardial dysfunction during paroxysmal supraventricular tachycardia. *Circulation* 1981;64:421–6.

19 Deal BV, Keane JF, Gillette PC, Garson A. Wolff Parkinson White syndrome and supraventricular tachycardia during infancy: management and follow-up. *J Am Coll Cardiol* 1985;5:130–5.

20 Laham J. Le syndrome de Wolff-Parkinson-White chez les enfants. *Med Infant* 1970;77:301–16.

21 Rossi L. A histological survey of preexcitation syndrome and related arrhythmias. *G Ital Cardiol* 1975;5:816–28.

22 Garson A, McNamara DG. Sudden death in a pediatric cardiology population, 1958 to 1983: relation to prior arrhythmias. *J Am Coll Cardiol* 1985;5:134B–7B.

23 Brembilla-Perrot B, Aliot F, Louis P, *et al.* Suivi de 195 patients atteints de syndrome de Wolff-Parkinson-White. *Arch Mal Coeur* 1987;80: 271–7.

Br Heart J 1987;58:96–100

Atrial natriuretic peptide in spontaneous tachycardias

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SUMMARY Because anecdotal reports suggest that concentrations of atrial natriuretic peptide are raised during tachycardias, plasma immunoreactive atrial natriuretic peptide concentrations were measured in 34 consecutive patients when tachycardia was diagnosed and again five and 15 minutes after conversion to sinus rhythm. Plasma atrial natriuretic peptide concentrations were raised in all but four patients, and were higher in patients with known heart disease than in those without. The concentrations were higher with ventricular tachycardia than with atrial fibrillation or supraventricular tachycardia, and in acute versus chronic tachycardia. There was only a weak positive relation between ventricular rate and atrial natriuretic peptide ($r = 0{\cdot}31$); but there was a closer inverse correlation between atrial natriuretic peptide and systolic arterial pressure ($r = -0{\cdot}60$). Conversion to sinus rhythm was associated with a definite fall in plasma atrial natriuretic peptide concentrations. Despite very high baseline concentrations of atrial natriuretic peptide only two patients reported polyuria. It is likely that atrial pressure rather than ventricular rate determines atrial natriuretic peptide release during tachycardia. Despite the absence of polyuria in all but two patients in this study atrial peptides could still contribute to, or cause, the polyuria of tachycardias.

Atrial natriuretic peptide is produced and stored by atrial myocytes,[1–3] and is released into plasma. The major circulating form in man appears to be the 28 amino acid α human atrial natriuretic peptide.[2] Animal experiments show that atrial natriuretic peptide secretion is increased by atrial stretch.[3 4] Incremental cardiac pacing stimulates atrial natriuretic peptide release in man,[5] and provisional reports suggest that atrial natriuretic peptide concentrations are increased during tachycardias.[6–9] Exogenous α human atrial natriuretic peptide in high dose has widespread actions in man including hypotension, diuresis, natriuresis, and suppression of certain vasoactive hormones.[10 11] Since tachycardias, particularly those of supraventricular origin, are not infrequently associated with a diuresis,[6 12 13] there is speculation that the urinary response may be mediated, at least in part, by atrial natriuretic peptide.

To define the relation between atrial natriuretic peptide and arrhythmias we measured plasma immunoreactive atrial natriuretic peptide concentrations in 34 consecutive patients presenting with spontaneous tachycardias.

Patients and methods

We studied 34 consecutive patients (mean (SE) 60 (3), range 29–84 years; 25 men, 9 women) presenting with spontaneous tachycardias which were converted to sinus rhythm. In 24 patients the tachycardia was acute (less than three days' duration, range 0·5 to 24 h) and in 10 it was chronic (more than three days' duration, range 6–100 days). Twenty four had documented cardiac disease (ischaemic heart disease in 18, dilated cardiomyopathy in 4, hypertension in 1, and mitral valve disease in 1).

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Fourteen patients had congestive heart failure before the arrhythmia. The remaining nine patients had no evidence of heart disease. Medication at the time of presentation was frusemide in 13 patients, an angiotensin converting enzyme inhibitor in nine, digoxin in 11, and an antiarrhythmic agent in six. Fifteen patients were not taking medications.

The arrhythmia was atrial fibrillation in 22 patients, re-entrant supraventricular tachycardia in five, and ventricular tachycardia in seven. Conversion to sinus rhythm was effected by direct current cardioversion in 18 patients and by pharmacological cardioversion (intravenous verapamil, lignocaine, or flecainide) in 13 subjects; it was spontaneous in the remaining three. Peripheral venous samples for the measurement of atrial natriuretic peptide were drawn immediately before the termination of the tachycardia and again five and 15 minutes after conversion to sinus rhythm. Blood was taken into chilled tubes containing edetic acid and Trasylol, rapidly centrifuged at +4°C, and the plasma stored at −80°C. Plasma was extracted with SepPak C18 cartridges before radioimmunoassay as described elsewhere.[14] The three samples for each patient were analysed in the same assay, but separate assays were used for samples from different patients. The intra-assay coefficient of variation was 10·1% and the inter-assay variability was 13·8%. We measured arterial pressure during the tachycardia with a standard mercury sphygmomanometer with the patient supine in bed.

Grouped data were compared by Student's *t* test and relations between indices were assessed by Pearson's product moment correlation coefficient. All results are given as mean (SEM).

Results

Ventricular rate during the tachycardia ranged from 70 to 220 beats/minute (mean 143 (7) beats/minute). The mean systolic arterial pressure was 116 (52) mm Hg (range 50–170 mm Hg). Plasma atrial natriuretic peptide concentrations before cardioversion were widely scattered between a minimum of 17 pmol/l and a maximum of 525 pmol/l (fig 1). In only four patients were baseline atrial natriuretic peptide concentrations within our normal range of 8–24 pmol/l. After conversion to sinus rhythm mean atrial natriuretic peptide concentrations fell to 116 (17) by five minutes and to 101 (19) pmol/l at 15 minutes (p < 0·01 and p < 0·02 respectively compared with initial concentrations). All but five patients had lower atrial natriuretic peptide concentrations 15 minutes after cardioversion than before. One patient showed a pronounced rise in atrial natriuretic peptide at 15 minutes after an initial decline (fig 1). There were no distinguishing clinical features to explain this anomalous response.

Baseline plasma atrial natriuretic peptide concentrations during tachycardia were higher in the 25 patients with heart disease (170 (28) pmol/l) than in the nine patients without heart disease (59 (21) pmol/l, p < 0·05; fig 2). Those with acute tachycardias had higher concentrations than patients with chronic tachycardias (163 (30) pmol/l and 88 (14) pmol/l respectively); however, the difference was

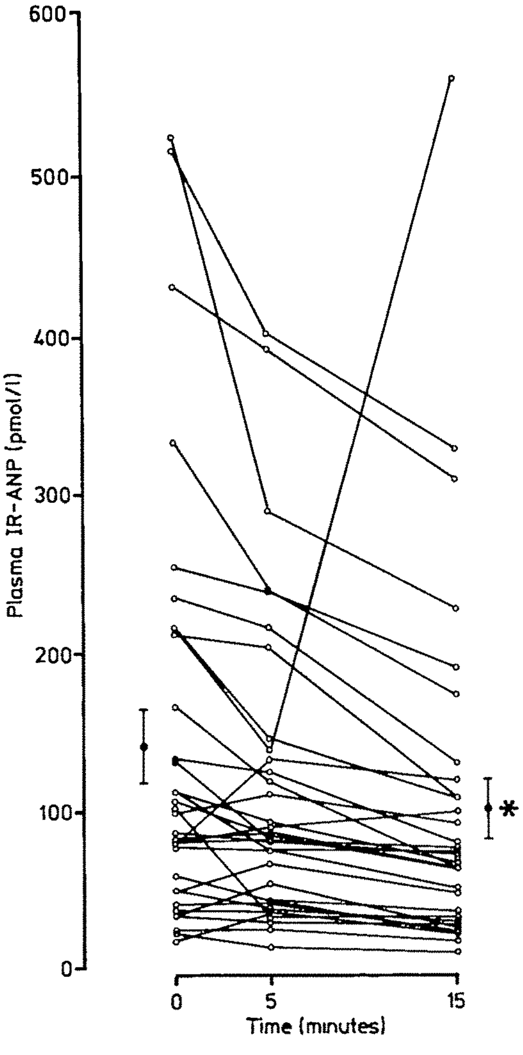

Fig 1 *Immunoreactive atrial natriuretic peptide (IR-ANP) concentrations in 34 patients with spontaneous tachycardia before (zero minutes) and 5 and 15 minutes after cardioversion. Data are shown for individuals and as mean (SEM).* *p < 0·02.

not statistically significant (fig 2). Ventricular tachycardia was associated with greater increase in atrial natriuretic peptide (332 (58) pmol/l) than atrial fibrillation (85 (11) pmol/l, $p < 0{\cdot}05$), or supraventricular tachycardia (120 (39) pmol/l, NS; fig 2). There was a positive, though weak, relation between the baseline ventricular rate and plasma atrial natriuretic peptide concentrations ($r = 0{\cdot}31$, NS). However, there was a statistically significant inverse correlation between plasma atrial natriuretic peptide concentrations and systolic arterial pressure before cardioversion ($r = 0{\cdot}60$, $p < 0{\cdot}001$; fig 3). Only two patients had a diuresis during the tachycardia; neither had cardiac disease or gross increases in plasma atrial natriuretic peptide (48 and 32 pmol/l). One of these patients presented with acute supraventricular tachycardia and the other with acute atrial fibrillation.

Discussion

This study confirms that plasma atrial natriuretic peptide concentrations are often raised in patients with spontaneous tachycardias. Despite the clear association between tachycardia and increased atrial natriuretic peptide concentrations, however, we observed only a weak statistical relation between atrial natriuretic peptide and ventricular rate before cardioversion. It seems unlikely, therefore, that ventricular rate itself is the proximate cause of atrial natriuretic peptide release. More likely, atrial natriuretic peptide release is mediated by associated haemodynamic changes and, in particular, the increase in atrial pressure. This is supported by the inverse correlation between baseline atrial natriuretic peptide concentrations and systolic arterial pressure, the latter being a crude index of haemodynamic derangements during the tachycardia. Further, patients with prior heart disease, many of whom have raised atrial natriuretic peptide concentrations,[15 16] would be expected to show greater increases in atrial pressure during tachycardia than patients with normal hearts, and indeed we found higher atrial natriuretic peptide concentrations in the patients with previous heart disease. Finally, ventricular tachycardias are likely to result in very high atrial pressures with canon waves,[17–19] and this group of patients had higher atrial natriuretic peptide concentrations than those with supraventricular tachycardias in whom atrial pressures would probably be lower.[20 21] The suggestion that atrial pressure or atrial stretch is the stimulus to

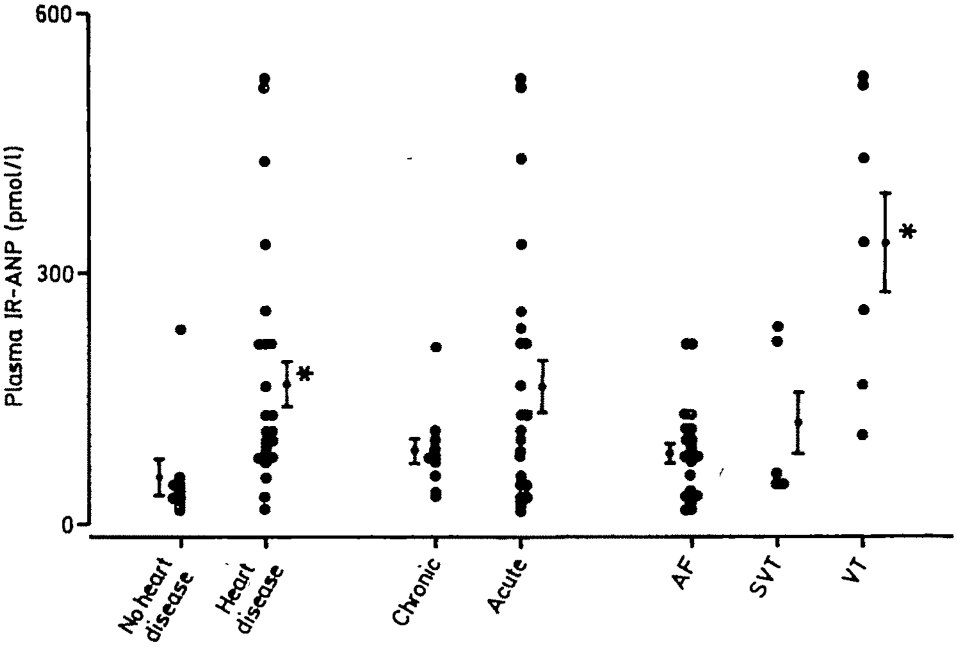

Fig 2 *Immunoreactive atrial natriuretic peptide (IR-ANP) concentrations in patients presenting with tachycardia. Results are shown for individuals and as mean (SEM). *p < 0·05: AF, atrial fibrillation; SVT, supraventricular tachycardia; VT, ventricular tachycardia.*

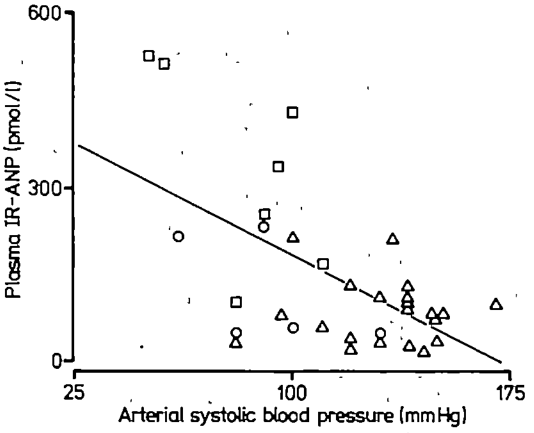

Fig 3 *Immunoreactive atrial natriuretic peptide (IR–ANP) concentrations and systolic arterial pressure in 33 patients presenting with tachycardia.* □, *ventricular tachycardia;* ○, *supraventricular tachycardia;* △, *atrial fibrillation. An additional patient did not have blood pressure recorded.* ($r = -0{\cdot}60, p < 0{\cdot}001.$)

atrial natriuretic peptide release during tachycardia is supported by the observations by Weil *et al* who reported a close positive association between right atrial pressure and plasma atrial natriuretic peptide concentrations during intracardiac pacing in man.[21] This is also consistent with animal data indicating that atrial stretch is an important, and perhaps the dominant stimulus, to release of atrial natriuretic peptide.[3 4] Although increased cardiac secretion of atrial natriuretic peptide may account in full for the high atrial natriuretic peptide concentrations we found during tachycardia it is possible that clearance of the peptide from plasma is delayed under these circumstances and that this too may contribute to the higher concentrations. This would be especially so when cardiac output falls sharply during the arrhythmia and blood flow to the kidneys and liver, organs where atrial natriuretic peptide is cleared,[5 16] is likely to decline precipitously. Little is known about the factors that regulate the clearance of atrial natriuretic peptide from plasma in man.

The half life of atrial natriuretic peptide, as determined from α human atrial natriuretic peptide infusion studies in healthy volunteers which used venous sampling, is approximately three minutes.[22] In the present study the fall in plasma atrial natriuretic peptide concentrations after cardioversion was slow, with an estimated half life well beyond three minutes. The probable explanation is that atrial pressures do not necessarily return to normal immediately sinus rhythm is restored.[23] In addition, some of our patients had cardiac failure before the onset of tachycardia, and atrial natriuretic peptide concentrations would not be expected to fall into the normal range. Finally, it is possible that the plasma clearance rate of atrial natriuretic peptide is reduced for some time after sinus rhythm is achieved.

There has been speculation that atrial peptides might account for the well-known association of diuresis with tachycardia.[6 7] None the less, all but five of our patients had high plasma atrial natriuretic peptide concentrations, yet only two noted polyuria. Further, plasma atrial natriuretic peptide concentrations in these two patients were not grossly increased. Superficially, this might be taken as evidence against a role for atrial peptides in the polyuria of tachycardias. Much more information is needed, however, on the factors which modify the urinary response to atrial natriuretic peptide before firm conclusions can be reached. Already it is known that the arterial pressure,[24–26] dietary sodium intake,[27] activity of pressor systems,[28] and the presence of heart failure[29] can modify the renal actions of administered atrial natriuretic peptide. It is possible, therefore, that a minor rise in plasma atrial natriuretic peptide concentrations during tachycardia in a patient whose arterial pressure is maintained will induce an appreciable diuresis. On the contrary, a much higher atrial natriuretic peptide concentration may fail to increase urine output in a patient with cardiac failure in whom ventricular tachycardia has induced profound hypotension.

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References

1 Kisch B. Electron microscopy of the atrium of the heart: guinea pig. *Exp Med Surg* 1956;**14**:99–112.
2 Kangawa K, Matsuo H. Purification and complete amino acid sequence of α-human atrial natriuretic polypeptide (α-hANP). *Biochem Biophys Res Commun* 1984;**118**:131–9.
3 Dietz JR. Release of natriuretic factor from rat heart-lung preparation by atrial distension. *Am J Physiol* 1984;**247**:R1093–6.
4 Ledsome JR, Wilson N, Courneya CA, Rankin AJ. Release of atrial natriuretic peptide by atrial distension. *Can J Physiol Pharmacol* 1985;**63**:739–42.
5 Crozier IG, Nicholls MG, Ikram H, Espiner EA, Yandle TG, Jans S. Atrial natriuretic peptide in man: production and clearance by various tissues. *Hypertension* 1986;**8**(suppl II):11–5.
6 Schiffrin EL, Gutkowska J, Kuchel O, Cantin M, Genest J. Plasma concentration of atrial natriuretic

factor in a patient with paroxysmal atrial tachycardia. *N Engl J Med* 1985;**312**:1196–7.

7 Tikkanen I, Metsarinne K, Fyhrquist F. Atrial natriuretic peptide in paroxysmal supraventricular tachycardia. *Lancet* 1985;**ii**:40–1.

8 Yamaji T, Ishibashi M, Nakaoka H, Imataka K, Amano M, Fujii J. Possible role for atrial natriuretic peptide in polyuria associated with paroxysmal atrial arrhythmias *Lancet* 1985;**i**:1211.

9 Anderson JV, Gibbs JSR, Woodruff PWR, Greco C, Rowland E, Bloom SR. The plasma atrial natriuretic peptide response to treatment of acute cardiac failure, spontaneous supraventricular tachycardia and induced re-entrant tachycardia in man. *J Hypertens* 1986;**4**(suppl 2):S137–41.

10 Richards AM, Nicholls MG, Ikram H, Webster MWI, Yandle TG, Espiner EA. Renal, haemodynamic, and hormonal effects of human alpha atrial natriuretic peptide in healthy volunteers. *Lancet* 1985;**i**:545–9.

11 Richards AM, Nicholls MG, Espiner EA, *et al.* Effects of α-human atrial natriuretic peptide in essential hypertension. *Hypertension* 1985;7:812–7.

12 Wood P. Polyuria in paroxysmal tachycardia and paroxysmal atrial flutter and fibrillation. *Br Heart J* 1963;**25**:273–82.

13 Kaye GC, Nathan AW, Camm AJ. Polyuria associated with paroxysmal tachycardia. *Clin Prog Pacing Electrophysiol* 1984;**2**:349–59.

14 Yandle TG, Espiner EA, Nicholls MG, Duff H. Radioimmunoassay and characterization of atrial natriuretic peptide in human plasma. *J Clin Endocrinol Metab* 1986;**63**:72–9.

15 Tikkanen I, Fyhrquist F, Metsarinne K, Leidenius R. Plasma atrial natriuretic peptide in cardiac disease and during infusion in healthy volunteers. *Lancet* 1985;**ii**:66–9.

16 Richards AM, Cleland JGF, Tonolo G, *et al.* Plasma α natriuretic peptide in cardiac impairment. *Br Med J* 1986;**293** 409–12.

17 Samet P, Bernstein WH, Levine S, Lopez A. Hemodynamic effects of tachycardias produced by atrial and ventricular pacing. *Am J Med* 1965;**39**:905–10.

18 Alicandri C, Fouad FM, Tarazi RC, Castle L, Morant V. Three cases of hypotension and syncope with ventricular pacing: possible role of atrial reflexes. *Am J Cardiol* 1978;**42**:137–42.

19 Erlebacher JA, Danner RL, Stelzer PE Hypotension with ventricular pacing: an atrial vasodepressor reflex in human beings. *J Am Coll Cardiol* 1984;**4**:550–5.

20 Luria MH, Adelson EI, Lochaya S. Paroxysmal tachycardia with polyuria. *Ann Intern Med* 1966;**65**: 461–70.

21 Weil J, Haufe M, Natzka K, *et al* Plasma atrial natriuretic peptide concentrations during intracardiac pacing. *Acta Endocrinol (Copenh)* 1986; **111**(suppl 274):164–5.

22 Yandle TG, Richards AM, Nicholls MG, Cuneo R, Espiner EA, Livesey JH. Metabolic clearance rate and plasma half life of alpha-human atrial natriuretic peptide in man. *Life Sci* 1986;**38**:1827–33.

23 Schlepper M, Weppner HG, Merle H. Haemodynamic effects of supraventricular tachycardias and their alterations by electrically and verapamil induced termination. *Cardiovasc Res* 1978;**12**.28–33.

24 Biollaz J, Nussberger J, Waeber B, Brunner HR. Clinical pharmacology of atrial natriuretic (3–28) eicosahexapeptide. *J Hypertens* 1986;**4**(suppl 2):S101–8.

25 Blaine EH, Heinel LA, Schorn TW, Marsh EA, Whinnery MA. The character of the atrial natriuretic response: pressure and volume effects. *J Hypertens* 1986;**4**(suppl 2):S17–24.

26 Sosa RE, Volpe M, Marion DN, *et al.* Relationship between renal hemodynamic and natriuretic effects of atrial natriuretic factor. *Am J Physiol* 1986; **250**:F520–4.

27 Cuneo RC, Espiner EA, Nicholls MG, Yandle TG, Joyce SL, Gilchrist NL. Renal, hemodynamic, and hormonal responses to atrial natriuretic peptide infusions in normal man, and effect of sodium intake. *J Clin Endocrinol Metab* 1986;**63**:946–53.

28 Trippodo NC, MacPhee AA, Cole FE. Natriuretic response to atrial natriuretic factor enhanced by angiotensin II and vasopressin. *J Hypertens* 1984;**2**(suppl 3):289–91.

29 Crozier IG, Nicholls MG, Ikram H, Espiner EA, Gomez HJ, Warner NJ. Beneficial haemodynamic effects of atrial peptide infusions in heart failure. *Lancet* 1986;**ii**:1242–5.

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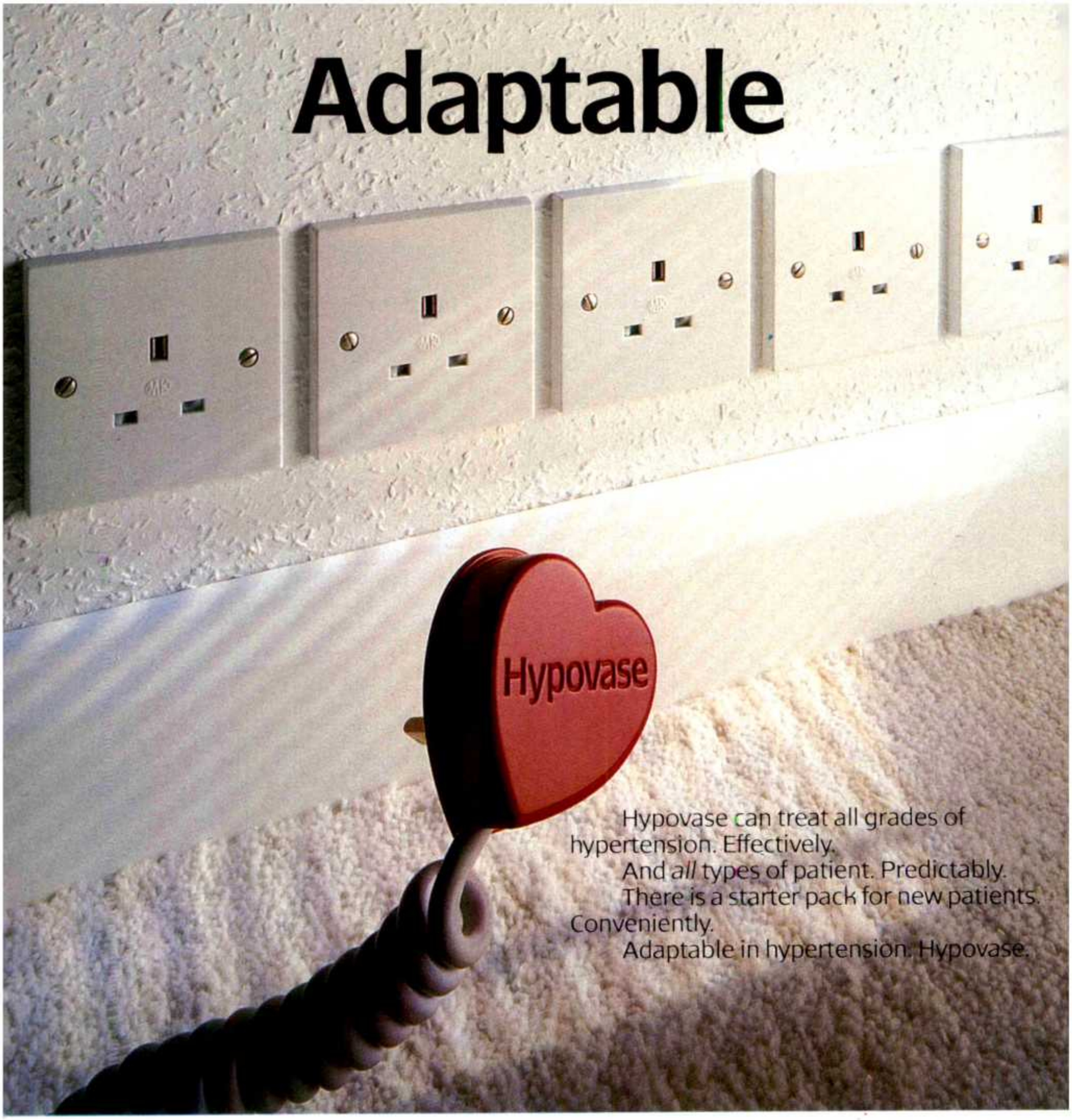

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Global and regional right ventricular function after acute myocardial infarction: dependence upon site of left ventricular infarction

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SUMMARY The relation of global and regional right and left ventricular function during the acute phase after a first myocardial infarction was assessed by first pass radionuclide angiography in 20 patients (10 after anterior and 10 after inferior myocardial infarction). The right ventricular ejection fraction did not differ significantly between the groups, but left ventricular ejection fraction was significantly depressed after anterior myocardial infarction. There was evidence of right ventricular dilatation and impaired transit in the group with inferior infarction. Five patients with anterior infarction and six with inferior infarction had abnormal right ventricular ejection fractions. Right ventricular wall motion abnormalities affected the septal wall in the group with anterior infarction and the free wall in the group with inferior infarction. The relation between right and left ventricular ejection fractions was markedly different in the two groups. In the group with anterior infarction there was a significant linear relation between right and left ventricular ejection fraction, whereas in the group with inferior infarction there was not.

Thus right ventricular dysfunction commonly occurs after both anterior and inferior myocardial infarction. Right and left ventricular impairment are related after anterior myocardial infarction, but are independent after inferior myocardial infarction. Finally, the different effects of anterior and inferior myocardial infarction on right ventricular function may be explained by differences in septal and free wall involvement.

Right ventricular dysfunction secondary to right ventricular myocardial infarction is now well recognised.[1] Invasive haemodynamic monitoring allows primary abnormalities of right ventricular function to be distinguished from those that are secondary to left ventricular dysfunction.[2] The right ventricular free wall is exclusively supplied by the right coronary artery,[3] and therefore most studies of right ventricular function after myocardial infarction have concentrated on patients with inferior infarction.

Rigo *et al* reported dilatation of the right ventricle after inferior infarction.[4] Since then there have been conflicting reports, with some investigators finding right ventricular dysfunction after inferior infarction but not after anterior infarction,[5 6] while others have found it in both groups.[7]

Since not only the right ventricular free wall but also the interventricular septum contribute to right ventricular contraction,[8] septal involvement in anterior infarction might be expected to cause some degree of right ventricular dysfunction. To assess the extent of right ventricular dysfunction after myocardial infarction and its relation to the site of left ventricular infarction we assessed global and regional right and left ventricular function in a population of patients admitted during the acute phase of their first myocardial infarction.

Patients and methods

PATIENTS

We studied 20 patients (19 men; mean (SD) age 53·8 (8·9), range 35–65 years) (table 1). They had no

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Table 1 *Clinical details and right and left ventricular indices in 20 patients with acute anterior or inferior infarction*

							RV			*LV*		
No	*Age*	*Sex*	*Site*	*Day*	*HR (beats/min)*	*Bolus (s)*	*Cyc*	*TT (s)*	*EF (%)*	*Cyc*	*TT (s)*	*EF (%)*
1	63	M	A	6	98	0·9	6	3·3	13	11	6·5	20
2	53	M	I	6	68	2·5	5	4·1	20	6	5·4	55
3	45	F	A	7	85	0·9	5	3·0	22	6	4·1	19
4	42	M	A	3	91	1·3	2	1·1	39	7	5·5	51
5	56	M	I	2	51	1·0	3	3·2	36	6	6·8	57
6	65	M	I	16	98	1·1	5	2·8	29	6	3·8	49
7	61	M	A	6	77	1·8	5	3·6	30	7	5·8	30
8	49	M	I	3	89	3·2	6	4·0	26	9	6·2	57
9	60	M	A	7	65	1·2	4	3·4	25	6	5·1	24
10	61	M	I	3	85	1·9	11	7·6	39	7	4·6	50
11	56	M	I	7	94	6·0	10	6·1	25	9	5·5	41
12	63	M	I	2	56	1·7	6	6·2	23	8	8·3	65
13	58	M	I	5	95	1·2	10	6·0	16	8	4·9	52
14	62	M	A	7	80	1·0	5	3·5	23	6	4·4	45
15	46	M	I	7	82	1·2	6	4·1	32	7	5·3	50
16	62	M	A	7	93	1·5	6	3·6	15	11	7·6	34
17	41	M	A	3	48	0·9	3	3·2	57	5	5·7	61
18	45	M	A	4	69	0·8	3	2·5	43	5	4·5	51
19	53	M	I	8	81	1·5	6	4·1	31	8	6·1	57
20	35	M	A	9	75	0·5	6	4·4	56	6	4·8	61
Mean (SD)	53·8 (8·9)			5·9 (3·2)	79 (15)	1·6 (1·2)	5·7 (2·4)	4·0 (1·5)	30 (12·2)	7·2 (1·7)	5·5 (1·1)	46·5 (13·9)

RV, right ventricular; LV, left ventricular; site, site of myocardial infarction; day, day of study post-infarction; HR, heart rate; bolus, bolus duration in the superior vena cava; cyc, cycles available for analysis; TT, transit time; EF, ejection fraction; A, anterior; I, inferior.

clinical or electrocardiographic evidence of a previous myocardial infarction. All presented with typical ischaemic chest pain, all developed electrocardiographic changes characteristic of a transmural myocardial infarction (ST segment elevation, T wave inversion, and Q waves), and all had diagnostic serial changes in serum cardiac enzymes. The infarction was defined as inferior if the electrocardiographic changes developed in leads II, III, and aVF, and as anterior if the changes occurred in any two consecutive leads from leads V1–V6. Patients were not included if the site of infarction could not be defined by this system. Patients were studied in the acute phase of infarction as soon as it was considered safe for them to be moved to the nuclear cardiology laboratory.

RADIONUCLIDE ANGIOGRAPHY

First pass radionuclide angiography was performed with a multicrystal gamma camera (Baird System-77) in the 30° right anterior oblique projection in supine resting patients as previously described.[9] An 18 gauge cannula was inserted into a medial antecubital fossa vein and 660 MBq of technetium-99m was injected for each study by rapid saline flush. Data were acquired for 30 s at 30 ms framing intervals.

DATA ANALYSIS

Global right ventricular function

Radionuclide bolus duration was assessed from time-activity curves derived from a region of interest over the superior vena cava.[10] Right ventricular ejection fraction was calculated by a previously described method.[11]

Heart rate, right ventricular transit time (defined as the duration of activity in the right ventricle), and right ventricular cycles were derived from the right ventricular time-activity curve, and the planar right ventricular area was derived from the right ventricular region of interest. This measure was included to allow comparison with the study of Rigo *et al*,[4] who used planar right ventricular area as an index of right ventricular dilatation.[4]

Global left ventricular function

Left ventricular ejection fraction and functional images were derived from high frequency time-activity curves by a standard software program as previously described.[9]

Regional left and right ventricular function

Regional wall motion was assessed from count-based regional ejection fraction images. These were derived from end systolic and end diastolic images, and showed the proportionate change in counts and hence the volume within each part of the ventricle. The left ventricular border was visually divided into three equal segments: anterior, apical, and inferior. A segment was deemed to be abnormal if more than half of it showed a regional ejection fraction of $<50\%$.[12] The right ventricle was arbitrarily divided into two equal segments. The inferior border from the tricuspid valve plane to the apex was defined as

Table 2 *Comparison of the results in patients with anterior and inferior myocardial infarctions. Results expressed as mean (SD)*

	Anterior (n = 10)	*Inferior (n = 10)*	*p value*
Age (years)	51·6(10·9)	56·0(6·0)	NS
Day	5·9(2·0)	5·9(4·2)	NS
Heart rate (beats/min)	78·1(14·9)	80·0(16·4)	NS
Bolus (s)	1·1(0·4)	2·1(1·5)	NS
RV area (cm^2)	38·4(12·2)	50·5(5·7)	<0·05
RV cycles	4·5(1·4)	6·8(2·6)	<0·05
RV TT (s)	3·2(0·9)	4·8(1·5)	<0·01
LV cycles	7·0(2·2)	7·4(1·2)	NS
LV TT (s)	5·4(1·1)	5·7(1·3)	NS
RVEF (%)	32·3(15·8)	27·2(7·1)	NS
LVEF (%)	39·6(16·3)	53·3(6·4)	<0·05

the "free wall" segment and the anterior border from the apex to pulmonary outflow tract was defined as the "septal" segment.[8]

Statistical analysis

The results are expressed as mean (SD). Results within a group were compared by paired *t* tests and results between groups by unpaired *t* tests. Correlation coefficients (r) were derived by a standard software program.

Results

ALL PATIENTS

Table 1 shows results in all patients. The patients were studied 5·9(3·2) days (range 2–16) after infarction. The number of right ventricular cycles (5·7(2·4)) that were available was significantly less than for the number of left ventricular cycles (7·2(1·7)) (p < 0·01). The transit time of the right ventricle (4·0(1·5)s) was significantly shorter than that of the left (5·5(1·1)s) (p < 0·001). The right ventricular ejection fraction was 30(12·2)% (range 13–56) and the left ventricular ejection fraction was 46·5(13·9)% (range 19–65) (p < 0·001). Eleven of 20 patients had a right ventricular ejection fraction of <30%. This represents our lower limit of normal derived from 21 normal volunteers without clinical or electrocardiographic evidence of heart disease.[13] Eight of the 20 patients had an abnormal left ventricular ejection fraction (<50%).

Table 3 *Right and left ventricular regional wall motion abnormalities after anterior and inferior myocardial infarction*

	Anterior (n = 10)	*Inferior (n = 10)*
Right ventricle:		
Normal	6	5
Septal	3	0
Free wall	0	4
Diffuse	1	1
Left ventricle:		
Normal	1	3
Anterior	2	0
Anteroapical	5	0
Apical	1	0
Inferior	0	5
Inferoapical	0	2
Diffuse	1	0

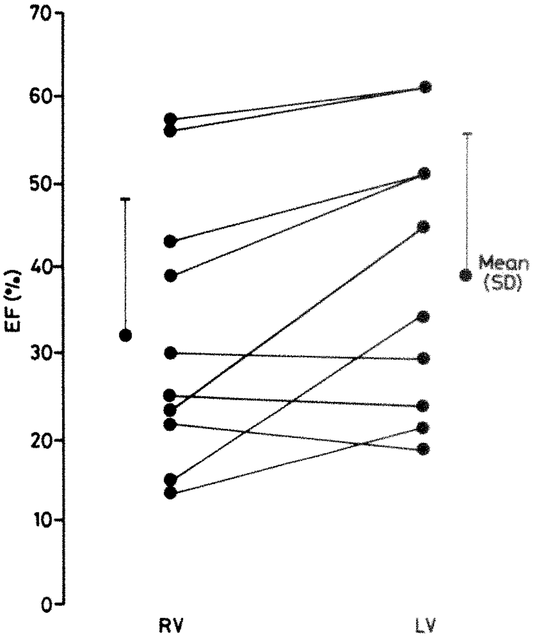

Fig 1 *Right (RV) and left (LV) ventricular ejection fractions (EF %) in the ten patients with anterior myocardial infarction. The values for each patient are joined by a solid line. Note the wide range of right and left ventricular ejection fractions.*

ANTERIOR MYOCARDIAL INFARCTION

Table 2 shows the results for the global variables of ventricular function and table 3 shows regional function. Right ventricular area was 38·4(12·2)cm^2. There were 4·5(1·4) cycles available for analysis of the right ventricle and 7·0(2·2) for the left ventricle (p < 0·01). Transit time was 3·2(0·9)s for the right ventricle and 5·4(1·1)s for the left ventricle (p < 0·001). Right ventricular ejection fraction was 32·3(15·8%) and left ventricular ejection fraction was 39·3(16·3)% (p < 0·05). Five of ten patients had abnormal right ventricular ejection fractions and six of ten had abnormal left ventricular ejection fractions. Figure 1 shows the ranges of right and left

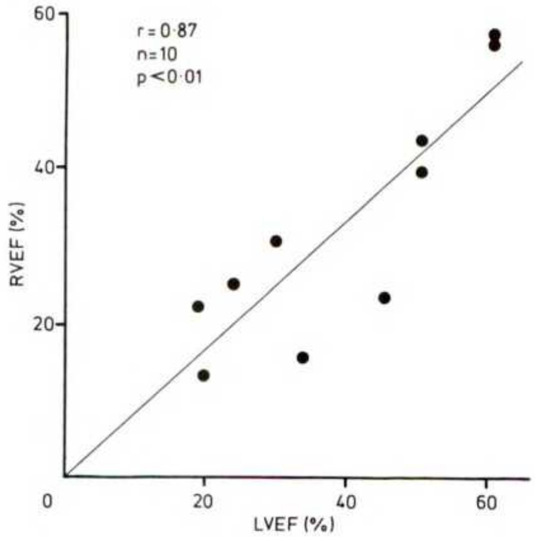

Fig 2 *Relation between right and left ventricular ejection fractions in 10 patients after anterior myocardial infarction. The line represents the best fit; the correlation coefficient (r) and corresponding p value are shown.*

ventricular ejection fractions in all patients. Figure 2 shows the relation between right and left ventricular ejection fractions. This shows a linear relation ($r = 0{\cdot}87$, $p < 0{\cdot}01$).

Table 3 lists the regional abnormalities; four of the five patients with abnormal right ventricular ejection fractions had regional right ventricular abnormalities. Nine patients, three with normal left ventricular ejection fractions, showed abnormalities of regional left ventricular function. Figure 3 shows the images in a patient with a small anterior infarction with normal right and left ventricular ejection fractions and normal regional wall motion. In contrast, fig 4 shows the images in a patient who had impaired right and left ventricular function after anterior infarction; this patient had septal right ventricular and anterior left ventricular wall motion abnormalities.

INFERIOR MYOCARDIAL INFARCTION

Tables 2 and 3 show the results in patients with inferior myocardial infarction. The mean right ventricular area was 50·5 (5·7)cm^2. There were 6·8 (2·6) cycles available for the right ventricle and 7·4 (1·2) for the left ventricle (p, NS). Transit time was 4·8 (1·5)s for the right ventricle and 5·7 (1·3)s for the left ventricle (p, NS). Right ventricular ejection fraction was 27·2 (7·1)% and left ventricular ejection fraction was 53·3 (6·4)% ($p < 0{\cdot}001$). Six of ten patients had abnormal right ventricular ejection fractions and two of ten patients had abnormal left ventricular ejection fractions. Figure 5 shows the right and left ventricular ejection fractions in all patients. Figure 6 shows the relation between right and left ventricular ejection fraction in this group. In contrast to the anterior infarction group there was no significant relation ($r = -0{\cdot}1$).

Table 3 lists the regional abnormalities. Five of the six patients with abnormal right ventricular ejec-

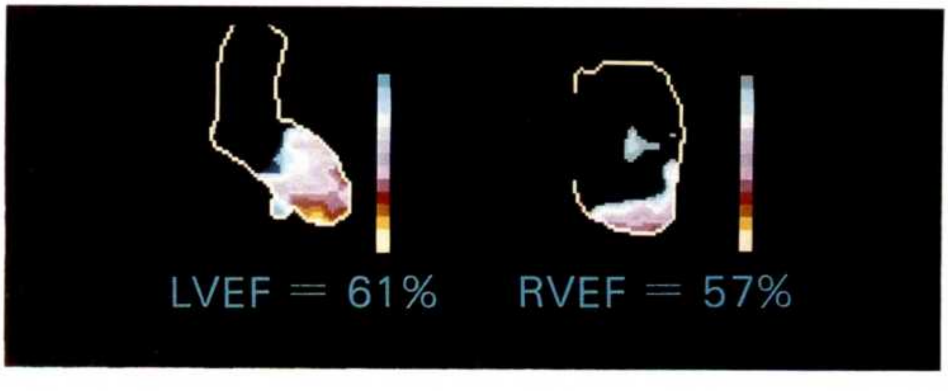

Fig 3 *Right and left ventricular regional ejection fraction images in a patient with a small anterior myocardial infarction. The colour scale shows regional ejection from yellow (100%); through orange, red, and blue to pale blues, and green; and finally black (0%). Each point on the scale represents a 6·25% change in regional ejection fraction. In this case the regional images are just within normal limits, although there is a small area of anterior hypokinesis just above the apex of the left ventricle.*

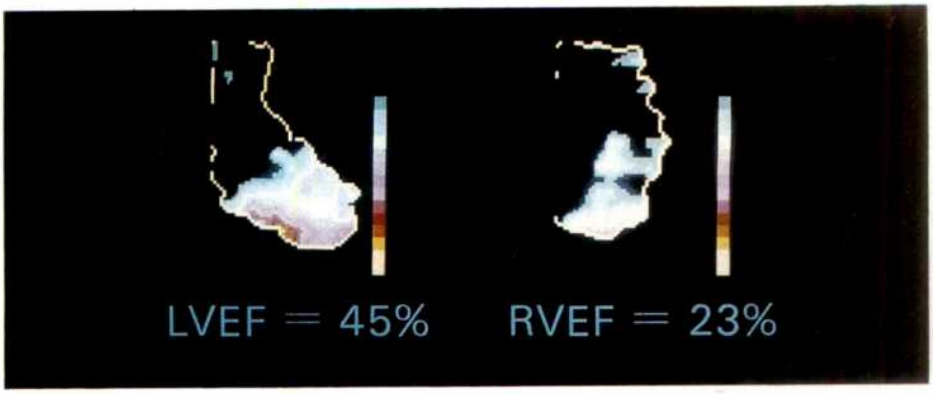

Fig 4 *Right and left ventricular regional ejection fraction images in a patient with an anterior myocardial infarction and associated septal right ventricular hypokinesis (right border). See fig 3 for colour scale.*

tion fractions had abnormalities of regional function. Seven patients had regional left ventricular abnormalities and two of these also had abnormal left ventricular ejection fractions. Figure 7 shows images in a patient with impaired right and left ventricular function after an inferior infarction. There was a right ventricular free wall abnormality and inferior left ventricular hypokinesis.

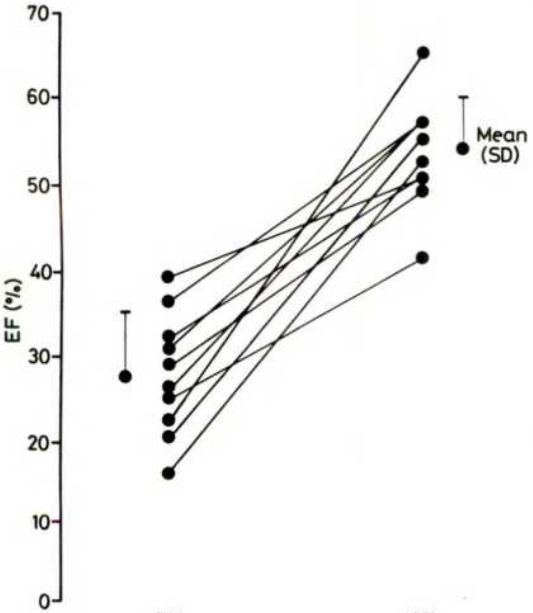

Fig 5 *Right and left ventricular ejection fractions in the ten patients with inferior myocardial infarctions. The format is the same as in fig 1. The range of right and left ventricular ejection fractions was much narrower than in the group with anterior myocardial infarction (fig 1).*

COMPARISON BETWEEN ANTERIOR AND INFERIOR MYOCARDIAL INFARCTION

There were no significant differences in age, day of study, heart rate, of radionuclide bolus duration in

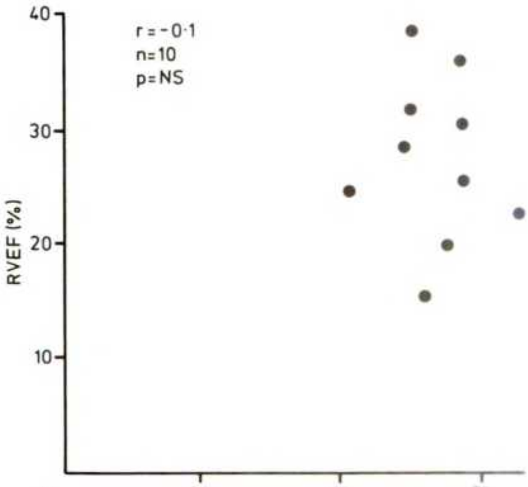

Fig 6 *Relation between right and left ventricular function in patients after inferior myocardial infarction.*

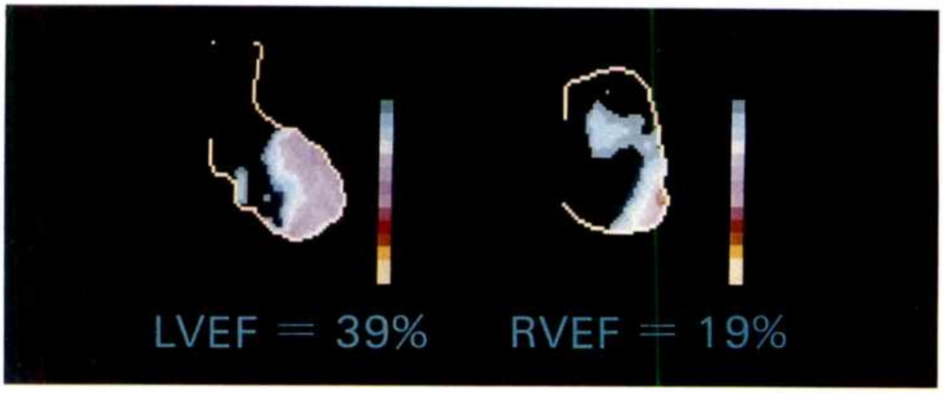

Fig 7 *Right and left ventricular images in a patient with inferior myocardial infarction associated with hypokinesis of the right ventricular free wall (inferior border) and the inferior left ventricle. See fig 3 for colour scale.*

the superior vena cava. The right ventricular area was significantly greater in the group with inferior infarction, suggesting right ventricular dilatation ($p < 0.05$). Both the number of right ventricular cycles available for analysis ($p < 0.05$), and, as a consequence of this, the right ventricular transit times ($p < 0.01$), were greater in the inferior infarction group. There were, however, no significant differences between the groups in left ventricular cycles and transit times. The right ventricular ejection fraction was lower in the inferior infarction group, but this failed to reach statistical significance when compared with the anterior infarction group. In contrast, the left ventricular ejection fraction was significantly lower in the group with anterior infarction ($p < 0.05$).

Regional abnormalities of both right and left ventricular function were common in both groups (table 3). However, abnormalities of regional right ventricular wall motion in the group with anterior infarction tended to involve the septal wall, whereas in the group with inferior infarction the free wall was predominantly involved. Regional abnormalities of the left ventricle affected the appropriate segment and were also dependent upon the site of the myocardial infarction. These abnormalities were present in all eight patients with abnormal left ventricular ejection fractions and also in eight patients with normal resting left ventricular ejection fractions.

Discussion

Although the clinicopathological syndrome of myocardial infarction has been known for at least a century,[14] dominant right ventricular involvement was first described within the past twelve years.[1] A study of 2000 consecutive necropsies found right ventricular infarction in 13·8%, the majority being associated with extension from a left ventricular infarction, but in 2·4% the infarction was confined to the right ventricle.[15] Other investigators found that the right ventricle was affected only when there was transmural inferior left ventricular infarction[16]; Ratliff and Hacket found that the right ventricle was affected in 34% of such patients.[17] Wade described 11 patients with right ventricular infarction all of whom had proximal occlusion of the right coronary artery.[18] This is not surprising since the right ventricular free wall, in man, is exclusively supplied by the right coronary artery.[3] It is now recognised, however, that free wall contraction contributes only part, and possibly a small part, of the total systolic volume change of the right ventricle. Contraction of the interventricular septum and the crista supraventricularis may be far more important than that of the free wall.[8] Since the interventricular septum receives blood from the left anterior descending coronary artery, right ventricular dysfunction might occur not only in patients with inferior infarction but also in those with anterior infarction.

In an early study Rigo *et al* showed that the ratio of right ventricular to left ventricular area after inferior infarction was higher than after anterior infarction, suggesting disproportionate dilatation of the right ventricle.[4] Other investigators found that the right ventricular ejection fraction was depressed in patients after inferior infarction but normal in patients after anterior infarction, with some individuals having values below the lower level of normal.[5 6] Steele *et al* found that all patients on the first day after inferior infarction had impaired right ventricular function that appeared to recover rapidly, whereas after anterior infarction only one third of patients developed transient abnormalities.[19] Marmor *et al* found impaired right ventricular function in patients after both inferior and anterior infarction, however, in contrast with Steele's data; this persisted in the group with inferior infarction but not in the group with anterior infarction.[7] In a prospective trial of 250 consecutive coronary care admissions, "predominant" right ventricular dysfunction was found in 43 and all of them had inferior infarction.[20] However, since only patients with nearly normal left ventricular function were included the selection was biased against patients with anterior infarction which causes greater depression of left ventricular ejection fractions.[7 19]

Since the first description of clinical right ventricular infarction there has been extensive work on the clinical,[1] electrocardiographic,[21] and haemodynamic[22] diagnosis of right ventricular infarction and dysfunction. There is often a discrepancy between the diagnosis of right ventricular infarction, primarily a histopathological finding, and right ventricular dysfunction, a clinical and pathophysiological entity. Thus it seems apparent that while right ventricular free wall infarction is related to inferior infarction and right coronary artery disease,[17] right ventricular dysfunction may occur independently of these features when it is associated with anterior infarction.[7 18]

We examined various variables of right and left ventricular function in a group of patients soon after infarction. Right ventricular ejection fraction was depressed in 55% of the patients and left ventricular ejection fraction in 40%. These figures are similar to those obtained in other studies.[4 5 7]

Left ventricular dysfunction (ejection fraction <50%) was more common in the group with anterior infarction (60%) than in the group with inferior infarction (20%). Right ventricular area was significantly smaller and right ventricular transit significantly more rapid in the group with anterior infarction than in the group with inferior infarction, despite the fact that not only the right ventricular ejection fraction but also the number of patients in each group with impaired global and regional right ventricular abnormalities were similar. The differences between the groups cannot be attributed to difference in timing of the studies because the mean study day was the same in both groups. These data confirm that right ventricular dilatation is disproportionately increased in patients with inferior infarction compared with anterior infarction and is associated with impaired transit. This may explain why the haemodynamic changes suggestive of dominant right ventricular dysfunction occur almost exclusively after inferior infarction.[20 22] In addition, as mentioned previously, left ventricular dysfunction is far more common in patients after anterior infarction,[7 19] and therefore isolated right ventricular dysfunction is far less likely to occur in this group.

Figures 2 and 5 show the relations between left and right ventricular ejection fractions in both groups. In patients with anterior infarction there is an impressive linear relation between right and left ventricular function. There are two possible explanations: firstly, that a large anterior infarction causes greater left ventricular ejection dysfunction, involves more of the interventricular septum, and therefore causes greater disturbance in right ventricular function; or alternatively, that a large anterior infarction produces a greater reduction in left ventricular ejection fraction, a greater increase in left ventricular diastolic filling pressure, and hence an increase in pulmonary arterial pressures and right ventricular afterload. The occurrence of regional rather than diffuse septal abnormalities of the right ventricle after anterior infarction tends to favour the former explanation.

In the group with inferior infarction there was no such relation between right and left ventricular ejection fractions. This is as expected since involvement of the free wall of the right ventricle may occur in the absence of a large inferior infarction,[16] and this was confirmed by the regional images. These data are similar to those of Marmor *et al* who also found a linear relation between right and left ventricular ejection fractions in patients with anterior infarction and no relation in those with inferior infarction. The equilibrium gated technique was used and they were less able to examine regional right ventricular performance, but right ventricular ejection fraction depression was related to the extent of septal involvement in anterior infarction.[7]

We studied only a small number of patients and thus our results must be interpreted with some care; however, there do appear to be significant differences between the two groups. The limitations of a static rather than mobile camera meant that only patients fit enough to be moved to the camera could be imaged. Thus while 85% of patients were imaged within one week of their myocardial infarction, imaging with a mobile gamma camera early after admission, that is, within 24 hours, might have produced different results. Steele *et al* initially imaged patients within 24 hours,[19] and Marmor *et al* within 48 hours of the onset of chest pain.[7] Since both of these studies suggested some improvement of right ventricular function with time, the present study may well underestimate the frequency of right ventricular dysfunction since no patient was imaged within two days of infarction. Development of mobile multicrystal cameras and single crystal cameras capable of performing first pass studies[23] will allow assessment in the coronary care unit. To date only three patients have proceeded to coronary angiography. It is therefore not yet possible to comment on the relation between global and regional right ventricular dysfunction and coronary anatomy.

We used the right anterior oblique projection for these studies. This is the ideal projection for the assessment of the right ventricle since right atrial overlap is minimised.[24] While it can be argued that the left anterior oblique projection provides the best separation of the right ventricular free wall and septal wall, this projection leads to maximal right atrial overlap of the right ventricle. Although the usefulness of regional wall motion images has been questioned, this study does suggest that information can be obtained on regional right ventricular dysfunction by this method.

These data confirm that right ventricular dysfunction is common in patients in the acute phase of myocardial infarction. They suggest an explanation for the predominance of patients with inferior infarction in studies of "dominant" right ventricular dysfunction. They also suggest that septal contribution to right ventricular contraction is far from negligible and they provide an explanation for the apparently minimal effects of isolated destruction of the right ventricular free wall in laboratory animals.[25 26] Because appropriate treatment for cardiogenic shock secondary to right ventricular dysfunction is most effective,[27] the ability to assess non-invasively global and regional right ventricular function in patients after myocardial infarction may prove important in the management of these patients.

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References

1 Cohn JN, Giuha NH, Broder MI, Limas CJ. Right ventricular infarction. Clinical and hemodynamic features. *Am J Cardiol* 1974;33:209–14.

2 Swan HJC, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with the use of a flow directed balloon-tipped catheter. *N Engl J Med* 1970;283:447–51.

3 Farrer-Brown G. Vascular pattern of myocardium of right ventricle of human heart. *Br Heart J* 1968;30:679–86.

4 Rigo P, Murray M, Taylor DR, *et al.* Right ventricular dysfunction detected by gated scintiphotography in patients with acute inferior myocardial infarction. *Circulation* 1975;52:268–74.

5 Reduto LA, Berger HJ, Cohen LS, Gottschalk A, Zaret BL. Sequential radionuclide assessment of left and right ventricular performance after acute transmural myocardial infarction. *Ann Intern Med* 1978;89: 441–7.

6 Tobinick E, Schelbert HR, Henning H, *et al.* Right ventricular ejection fraction in patients with acute anterior and inferior myocardial infarction assessed by radionuclide angiography. *Circulation* 1978;57: 1078–84.

7 Marmor A, Geltman EM, Biello DR, Sobel BE, Siegel BA, Roberts R. Functional response of the right ventricle to myocardial infarction: dependence on the site of left ventricular infarction. *Circulation* 1981;64: 1005–11.

8 James TN. Anatomy of the crista supraventricularis: its importance for understanding right ventricular function, right ventricular infarction and related conditions. *J Am Coll Cardiol* 1985;6:1083–95.

9 Dymond DS, Jarritt PH, Britton KE, Spurrell RAJ. Detection of postinfarction left ventricular aneurysms by first pass radionuclide ventriculography using a multicrystal gamma camera. *Br Heart J* 1979;41:68–78.

10 Dymond DS, Elliot A, Stone D, Hendrix G, Spurrell R. Factors that affect the reproducibility of left ventricular function from first-pass radionuclide angiograms. *Circulation* 1982;65:311–22.

11 Dymond DS, Grenier RP, Schmidt DH. Right ventricular ejection fraction from first-pass radionuclide angiograms: comparison with right ventriculography [Abstract]. *J Nucl Med* 1981;22:P23.

12 Dymond DS, Foster C, Grenier RP, Carpenter J, Schmidt DH. Peak exercise imaging for the detection of left ventricular function abnormalities in coronary artery disease. *Am J Cardiol* 1984;53:1532–7.

13 Caplin JL, Dymond DS, Maltz MB, O'Keefe JC, Flatman WD, Spurrell RAJ. Right ventricular function at rest and exercise in normals [Abstract]. *Clin Sci* 1985;68 (suppl 11):44P.

14 Lie JT. Centenary of the first correct antemortem diagnosis of coronary thrombosis by Adam Hamer (1818–78): English translation of the original report. *Am J Cardiol* 1978;42:849–52.

15 Wartmann WB, Hellerstein HF. The incidence of heart disease in 2000 consecutive autopsies. *Ann Intern Med* 1948;28:41–54.

16 Isner JM, Roberts WC. Right ventricular infarction complicating left ventricular infarction secondary to coronary heart disease. *Am J Cardiol* 1978;42: 885–94.

17 Ratliff NB, Hacket DB. Combined right and left ventricular infarction. Pathogenesis and clinicopathological correlation. *Am J Cardiol* 1980;45: 217–21.

18 Wade WG. The pathogenesis of infarction of the right ventricle. *Br Heart J* 1959;21:545–54.

19 Steele P, Kirch D, Ellis J, Vogel R, Battock D. Prompt

return to normal of depressed right ventricular ejection fraction in acute inferior infarction. *Br Heart J* 1977;**39**:1319–23.
20 Shah PK, Maddahi J, Berman DS, Pichler M, Swan HJC. Scintigraphically detected predominant right ventricular dysfunction in acute myocardial infarction: clinical hemodynamic correlates and implication for therapy and prognosis. *J Am Coll Cardiol* 1985;**6**:1264–72.
21 Erhardt LR, Sjögren A, Wahlberg J. Single right-sided precordial lead in the diagnosis of right ventricular involvement in inferior myocardial infarction. *Am Heart J* 1976;**91**:571–6.
22 Lopez-Sendon J, Coma-Canella I, Gamello C. Sensitivity and specificity of hemodynamic criteria in the diagnosis of acute right ventricular infarction. *Circulation* 1981;**64**:515–25.
23 Flatman WD, Dymond DS, O'Keefe J, Caplin J, Dyke LJ. First-pass measurement of global and regional left ventricular function using a digital single crystal camera: comparison with a multicrystal camera. *Nuklearmedizin* 1984;**21**:182–4.
24 Ferlinz J. Measurement of right ventricular volumes in man from single-plane cineangiograms. *Am Heart J* 1977;**94**:87–90.
25 Starr I, Jeffers WA, Medde RH. The absence of conspicuous increments in venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relationship between congestive cardiac failure and heart disease. *Am Heart J* 1943;**26**:291–301.
26 Guiha NH, Limas CJ, Cohn JN. Predominant right ventricular dysfunction after right ventricular destruction in the dog. *Am J Cardiol* 1974;**33**:254–8.
27 Cohn JN. Right ventricular infarction revisited. *Am J Cardiol* 1979;**43**:666–8.

Br Heart J 1987;58:110–15

Coronary sinus pH during percutaneous transluminal coronary angioplasty: early development of acidosis during myocardial ischaemia in man

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SUMMARY Coronary sinus pH was measured continuously in eight patients undergoing angioplasty to the left anterior descending coronary artery. A catheter tip pH sensitive electrode with a response time of less than 300 ms and an output ≥57 mV/pH unit was placed high in the coronary sinus. Recordings were obtained during a total of 24 balloon occlusions of the left anterior descending coronary artery varying in duration from 5 to 45 s. Continuous 12 lead surface electrocardiograms were recorded. During or after balloon inflation of ≤12 s (n = 4) there was no change in coronary sinus pH or the electrocardiogram. During balloon inflation of ≥15 s (n = 20) coronary sinus pH was unaltered but between 4 and 6 s after balloon deflation coronary sinus pH fell transiently by between 0·010 and 0·120 pH units before returning to the control value within 65 s. Ischaemic changes were seen on the electrocardiogram during 15 balloon occlusions. In individual patients the peak fall in coronary sinus pH was related to the duration of occlusion of the left anterior descending coronary artery. A rise in coronary sinus pH (alkalosis) was never seen.

In man acidosis occurs in the myocardium after short periods (≥12 s) of ischaemia. The fall of pH precedes ischaemic changes on the surface electrocardiogram and occurs concurrently with the earliest reported changes in contractile function.

The cause of the early decline in contractile function during myocardial ischaemia is not well understood but is almost certainly multifactorial.[1] Although the tissue content[2] of high energy phosphates, in particular creatine phosphate, is reduced, the magnitude of the fall in the free energy change of ATP hydrolysis is insufficient to depress contractility until several minutes of ischaemia have elapsed.[3] Alternative mechanisms have been proposed and some of these relate not to the lack of oxygen and substrate supply that occurs during ischaemia but to the retention of the products of metabolism, notably phosphate[4–6] and hydrogen ions (acidosis).[7–9]

Acidosis is known to depress the contractile function of the heart[10–12] and has been put forward as a mechanism for the loss of function early after the onset of myocardial ischaemia.[7 9] This hypothesis has been disputed[13 14] partly because the mechanism for the occurrence of an acidosis is uncertain and partly because of difficulties in quantifying the severity and rate of onset of acidosis in ischaemia. Under some experimental conditions acidosis and contractile failure were dissociated.[13 14] Early during hypoxia and ischaemia an alkalosis was reported.[15 16] If the retention of hydrogen ions and subsequent intracellular acidosis is an important cause of contractile dysfunction, then it is necessary to show that the acidosis is both sufficiently large and rapid in onset to account for at least part of the early decline in contractility.

Percutaneous transluminal coronary angioplasty provides a unique opportunity to study the early ionic changes during myocardial ischaemia in man and thus allow a comparison with results previously obtained during transient coronary occlusion in animals. This study was designed to determine the time

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of onset and severity of acidosis in the human myocardium during acute myocardial ischaemia. We have continuously measured changes in coronary sinus pH during repeated episodes of balloon occlusion of the left anterior descending coronary artery using rapidly responding pH sensitive electrodes.

Patients and methods

We studied eight patients (5 men, 3 women; aged 44–71, mean 53 years) with effort related angina pectoris who were already scheduled for routine percutaneous transluminal coronary angioplasty of the left anterior descending coronary artery. Patients with a recent myocardial infarction or chest pain at rest were excluded. All patients developed chest pain and significant ST segment depression ($\geqslant 1$ mm planar or downsloping 80 ms after the J point) during treadmill exercise by a modified Bruce protocol. All were in sinus rhythm with no conduction abnormalities or evidence of other cardiac abnormality apart from ischaemic heart disease. No patients were taking digoxin or antiarrhythmic medication. All patients were receiving nifedipine 10 mg three times daily but no other antianginal medication had been prescribed for at least 24 hours. Five patients had left anterior descending coronary artery disease only, one had additional left circumflex disease, and two had three vessel disease. Written informed consent was obtained in all cases and the study was approved by the ethics committee of the National Heart and Chest Hospitals.

pH ELECTRODES

Intravascular pH monitoring at any site other than a peripheral vein or artery requires an electrode at the tip of a flexible catheter which can be inserted into a vessel and left in situ. The construction and use of pH[17] and potassium[18] sensitive electrodes suitable for intravascular recording have been described. The pH sensitive ligand tridodecyclamine (Fluka AG, Switzerland) was used in these experiments rather than OCPH (*p*-octydecyloxy m-chlorophenyl hydrazone mesoxalonitrile), which was used in our earlier studies.[17 19 20] The electrode was inserted through a standard cardiac catheter (8 French thin-walled Cournand, USCI, USA). At the proximal end the electrode passed through a sliding adapter with a side arm (SFLL PCF MLL RA45°, Cook, UK). The space in the catheter around the electrode was filled with a heparinised saline solution and a calomel reference electrode (K4112, Radiometer, Sweden) was connected through a T-piece to the side arm of the adapter. The column of saline surrounding the pH electrode within the cardiac catheter thus acted as a salt bridge to connect the reference electrode to the bloodstream and it also provided coaxial electrical screening for the pH electrode.

The potential difference between the silver/silver chloride wire within the pH electrode and the calomel electrode was measured by a high impedance input amplifier (LF 352D National Semiconductor, Japan). The signal was passed through an optical isolator (3650 HG Burr Brown, Arizona, USA), to prevent leakage currents running to earth through the intravascular electrode, and through a 2 Hz filter. It was displayed on a pen recorder and recorded on magnetic tape.

The membrane resistance was $10^9\,\Omega$. The pH response of the electrodes was linear between pH 6·5 and 8·0 and the output at 37°C was between 57 and 59 mV/pH unit. The response time was less than 300 ms. The electrode was unresponsive to flow, blood pressure, Po_2, or osmolality (100–400 mmol/l). There was no cross sensitivity to Na^+ (100–200 mmol/l), K^+ (0–10 mmol/l), Ca^{2+} (0–10 mmol/l), or Mg^{2+} (0–10 mmol/l). It was not affected by changing the bicarbonate concentration (10–50 mmol/l) or carbon dioxide tension (20–100 mm Hg) at constant pH. The electrode stabilised in vivo in less than 15 minutes, and thereafter the drift was less than 0·005 pH units/hour. The electrode could detect changes as small as 0·005 pH units.

The electrodes were sterilised by immersion in an aqueous glutaraldehyde solution for one hour. The function of the electrodes was not affected by this process. Electrodes were calibrated before and after the entire procedure. Results were only accepted if there was no change in calibration. This procedure lead to the rejection of results in only one patient. Blood samples were obtained for determination of the absolute value of pH from the coronary sinus before insertion of the electrode into the catheter and at the end of the procedure.

STUDY PROTOCOL

One hour after premedication with lorazepam (1–2 mg orally) the Cournand catheter was inserted into the left subclavian vein and positioned in the coronary sinus just proximal to the great cardiac vein. The position was checked by the injection of contrast medium (Omnipaque 300, Nycomed (UK)). A pH electrode was introduced through the lumen of this catheter until the tip protruded 1 cm from the end of the catheter. The output from the electrode was allowed to stabilise for at least 20 minutes before angioplasty. pH was recorded continuously together with a standard 12 lead electrocardiogram until the end of the procedure.

Percutaneous transluminal angioplasty was performed from the right femoral artery with coronary guiding catheters and Simpson-Roberts coronary balloon dilatation catheters from Advanced Cardiovascular Systems Inc., California, USA. The number of balloon inflations required to dilate the vessel varied between 2 and 5 (mean (SEM) 3·0(0·5)). Inflation lasted from 8 to 45 s (mean (SEM) 24·8(2·8) s). Clinical considerations alone determined the number and duration of balloon inflations.

Results

pH CHANGES IN BLOOD FROM THE CORONARY SINUS

Figure 1 shows a recording of changes in coronary sinus pH during three successive balloon inflations. No change in coronary sinus pH was seen during the period of occlusion of the anterior descending coronary artery by the inflated balloon. When blood flow was restored by deflation of the balloon there was a transient fall in coronary sinus pH after a delay of 4–6 s. In one coronary occlusion (the second inflation in fig 1), where balloon inflation was initiated before the signal had returned to the baseline, the blood pH continued to return to the baseline during the early part of the inflation, indicating that some blood flow was present in the great cardiac vein during the period that the left anterior descending coronary artery was occluded (fig 1).

The peak pH change in an individual patient was related to the duration of coronary artery occlusion (fig 2). Four patients had an episode of coronary artery occlusion lasting < 12 s. Coronary sinus blood pH did not fall after these short episodes of coronary artery occlusion (fig 3). pH fell after all other episodes (all $\geqslant 15$ s) of occlusion (fig 3). The maximum change in coronary sinus blood pH was 0·120 pH units. Coronary sinus pH returned to control values within 65 s. The fall in pH seen in the eight patients was wide (fig 3). No rise of pH (alkalosis) was observed after any episode of coronary artery occlusion. A small (0·020 pH units) transient fall in pH was seen after injection of contrast medium (Omnipaque 300, Nycomed (UK) (pH 7·2)) into the left coronary artery (fig 1).

ELECTROCARDIOGRAPHIC CHANGES

ST segment elevation was > 1 mm in at least one precordial lead during 15 balloon inflations, all lasting more than 20 s (fig 3). Ischaemic electrocardiographic changes did not occur during the four balloon inflations lasting $\leqslant 12$ s after which no pH change occurred. Five balloon occlusions of the coronary artery which were followed by a fall in coronary sinus pH were not accompanied by electrocardiographic changes. Heart rate did not change significantly from the control value during or after occlusion of the vessel.

Discussion

Percutaneous transluminal coronary angioplasty provides the opportunity to study the early metabolic and physiological effects of coronary occlusion in man. The results of this study show that in the human myocardium acidosis develops after 12 to 15 s of coronary occlusion. Measurements were made with fast responding catheter tip pH electrodes which would detect changes of pH that might be missed by conventional sampling techniques. The electrode is stable, can detect pH changes of less than 0·005 pH units, and is free from cross sensitivity to other ions.

The pH of coronary sinus blood did not change during coronary occlusion. The concentration of hydrogen ions in the coronary sinus blood rose transiently when the blood flow was restored. This is attributable to washout of hydrogen ions generated

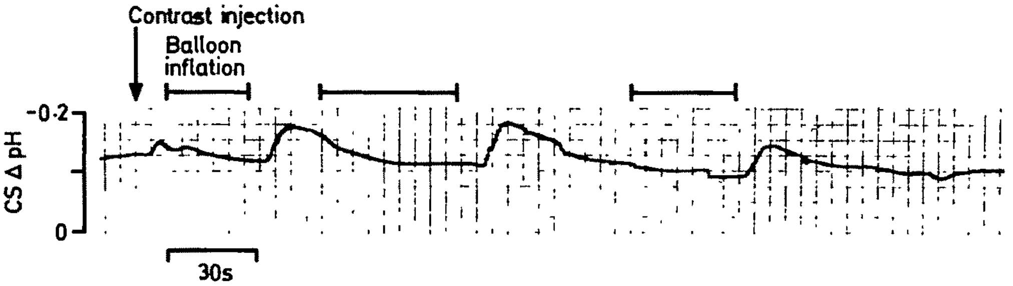

Fig 1 *Continuous recording of coronary sinus pH during three consecutive balloon occlusions of the left anterior descending coronary artery and one injection of contrast into the left coronary artery. Coronary sinus pH did not fall during balloon inflation but fell transiently 4 to 6 s after balloon deflation. Passage of contrast medium through the coronary circulation caused an abrupt transient fall in pH.*

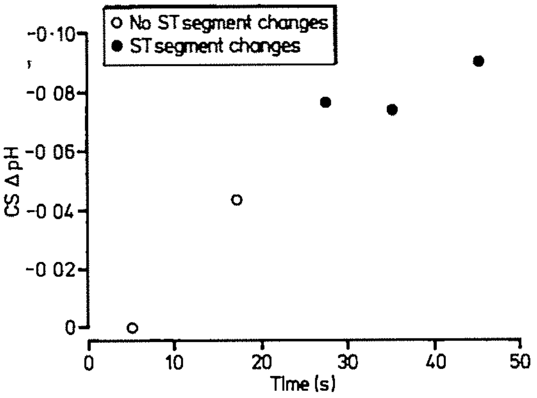

Fig 2 *Relation between the peak fall in coronary sinus pH and the duration of balloon occlusion of the left anterior descending coronary artery in one patient*

within the ischaemic tissue. Reduced arterial flow in the ischaemic area causes the retention of the end products of anaerobic metabolism in the tissue and such metabolites are removed from the myocardium when flow is restored. The small quantity of metabolites that might diffuse out from the edge of the ischaemic tissue during the period of ischaemia will be diluted by the coronary venous effluent from non-ischaemic myocardium, and the magnitude of any such change must either be too small to be detected or must be absent. The catheter was placed high in the coronary sinus so as to sense blood from the area of myocardium subserved by the occluded anterior descending coronary artery. Figure 1 shows there can be residual flow in the distal great cardiac vein during occlusion of the left anterior descending coronary artery; on the second inflation (initiated before the signal had returned to baseline) blood pH continued to return to the baseline value during the early part of the occlusion. The mechanism underlying this is unclear but it is probably related to hydrogen ions being washed out of the local coronary veins and great cardiac vein by blood flowing into them from the non-ischaemic area. It is unlikely to be due to a flow of blood from the ischaemic area, otherwise we would have observed a fall in pH during the latter part of balloon inflation.

After deflation of the balloon and hence restoration of blood flow, the coronary sinus pH fell after a delay of 4–6 s. The delay is due partly to the time required for collapse of the balloon and partly to the time taken by the hydrogen ions to diffuse from the intracellular and extracellular spaces into the blood and for the blood to reach the pH electrode. A similar delay has been reported in the dog.[19] Consistent with our findings others have reported a rise in the concentration of lactate in coronary sinus on balloon deflation after angioplasty.[20] Heart rate did not change during balloon inflation, so the observed change in pH was due to myocardial ischaemia induced by coronary artery occlusion and was not the result of an increase in heart rate causing ischaemia. Previous work has shown that ischaemia caused by atrial pacing in man is associated with a minor degree of acidosis during the pacing test and a washout of hydrogen ions immediately the test is stopped.[21]

The implications of these results depend on the validity of coronary sinus pH as an indirect indicator of changes in intracellular pH. We have continuously measured coronary sinus pH in this study and this avoids the errors that are introduced by sampling techniques. The time at which blood samples are taken after balloon deflation will have a profound effect on the magnitude of the pH changes, as fig 1 shows. Earlier studies have used changes in coronary sinus lactate as a marker of ischaemia but, unlike pH, lactate cannot be measured continuously and so is subject to the considerable errors that sampling introduces. It is not possible, without continuous measurement of regional coronary flow and coronary sinus blood flow and knowledge of the degree of mixing of blood from ischaemic myocardium with that from non-ischaemic myocardium, to calculate the precise quantity of hydrogen ions lost from a given amount of ischaemic myocardial tissue. These variables were not measured in this study. Blood in the coronary sinus will be subject to some dilution of hydrogen ions because blood from the ischaemic area will have mixed with that from the non-ischaemic

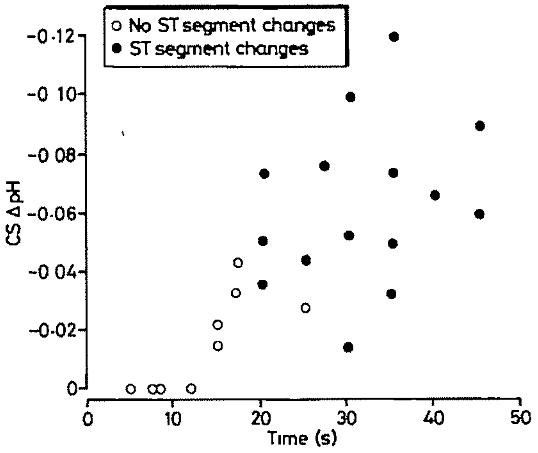

Fig 3 *Peak coronary sinus pH changes after all balloon occlusions of the left anterior descending coronary artery No change in pH occurred after balloon occlusion of* <12 *s.*

area, and any measured change in blood pH will necessarily be smaller than that present in the extracellular space of the ischaemic myocardium. We attempted to minimise these effects by placing the electrode high in the coronary sinus just proximal to the great cardiac vein. Furthermore, hydrogen ions are buffered by tissue buffer systems and by blood.

The magnitude of the pH changes that we have observed varied widely between patients. This can be explained in terms of the extent and severity of myocardial ischaemia and the magnitude of the collateral flow and flow through the reperfused native circulation. In individual patients the magnitude of the fall in coronary sinus pH was related to the duration of ischaemia (fig 2). The observed fall of pH in blood in the coronary sinus is likely to indicate the minimum change of intracellular pH. Cobbe *et al* have shown that in the dog the maximum fall of coronary sinus pH occurred 20 to 30 s after reperfusion and approximated to the maximum fall of tissue pH which also occurred 20–30 s after reperfusion.[19]

Our findings are consistent with those in animal experiments. Studies in dogs have shown that a fall in the pH of coronary sinus blood falls after coronary occlusions lasting >20 s.[19] Other workers using intracellular dyes[22] and rapidly responding extracellular pH electrodes[9] have reported a fall in pH within 5 s.

An important question is whether the changes in pH are large enough to cause contractile dysfunction. Cobbe and Poole-Wilson found that in the rabbit heart a fall in tissue pH of 0·03 units could contribute to a substantial fall (>30%) in muscle tension.[9] The changes in coronary sinus pH in the present study (fig 3) ranged from 0·015 to 0·075 pH units after balloon occlusions of between 17 and 20 s and from 0·025 to 0·120 pH units after balloon occlusions of between 25 and 45 s. If we assume that the peak fall in coronary sinus pH is similar to the peak fall in tissue pH,[19] then the magnitude of the fall in pH would be sufficient to cause important contractile dysfunction.[1,3,8,9,12]

Ventricular function has previously been assessed during coronary angioplasty.[21,23] After coronary occlusion the myocardium contracts normally for at least four beats. There is sufficient oxygen in the blood and myoglobin to provide the energy for at least two beats and after this anaerobic metabolism is stimulated. Impaired contractility can be detected between the fifth and twentieth beat. The exact time of these changes will vary from patient to patient and will depend on many factors. The duration of the monophasic action potential in man has also been reported to change after about 10 beats.[24] We have already shown that potassium is lost from the myocardium after approximately 12 beats.[18] Thus acidosis and potassium loss in man appear at the same time as the earliest changes in the configuration of the action potential and in contractile function.

The mechanism for the development of an acidosis is complex. The conversion of creatine phosphate to creatine consumes hydrogen ions and would be expected to cause an alkalosis. Under some experimental conditions this has been reported.[15,16] The breakdown of adenosine triphosphate (ATP) generates hydrogen ions but ATP is not greatly reduced early in ischaemia[2,3] The major mechanism for the early appearance of acidosis is stimulation of glycogenolysis.[25]

These studies show that in the human heart acidosis develops early after the onset of ischaemia and is of sufficient magnitude to contribute to the decline of contractility.

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References

1 Poole-Wilson PA, Fleetwood G, Cobbe SM. Early contractile failure in myocardial ischaemia—role of acidosis. In: Refsum H, Jynge P, Mjos OD, eds. *Myocardial ischaemia and protection*. Edinburgh: Churchill Livingstone, 1983:9–17.

2 Gudbjarnason S, Mathes P, Ravens KG. Functional compartmentation of ATP and creatine phosphate in heart muscle. *J Mol Cell Cardiol* 1970;1:325–39.

3 Kentish JC, Allen DG. Is force production in the myocardium directly dependent upon the free energy change of ATP hydrolysis? *J Mol Cell Cardiol* 1986;18:879–82.

4 Kübler W, Katz AM. Mechanisms of early "pump" failure of the ischaemic heart: possible role of adenosine triphosphate depletion and inorganic phosphate accumulation. *Am J Cardiol* 1977;40:467–71.

5 Kentish JC. The effects of inorganic phosphate and creatine phosphate on force production in skinned muscles from rat ventricle. *J Physiol (Lond)* 1986;370:585–604.

6 Herzig JW, Peterson JW, Ruegg JC, Solaro RJ. Vanadate and phosphate ions reduce tension and increase cross-bridge kinetics in chemically skinned heart muscle. *Biochem Biophys Acta* 1981;672:191–6.

7 Tennant R. Factors concerned in the arrest of contraction in an ischaemic myocardial area. *Am J Physiol* 1935;113:677–82.

8 Poole-Wilson PA. Measurement of myocardial intracellular pH in pathological states. *J Mol Cell Cardiol* 1978;10:511–26.

9 Cobbe SM, Poole-Wilson PA. The time of onset and severity of acidosis in myocardial ischemia. *J Mol Cell Cardiol* 1980;12:745–60.

10 Gaskell WH. On the tonicity of the heart and blood vessels. *J Physiol (Lond)* 1880;3:48–75.

11 Smith HW. The action of acids on turtle heart muscle

with reference to the penetration of anions. *Am J Physiol* 1926;76:411–47.

12 Poole-Wilson PA, Langer GA. Effect of pH on ionic exchange and function in rat and rabbit myocardium. *Am J Physiol* 1975;229:570–81.

13 Couper GS, Weiss J, Hiltbrand B, Shine KI. Extracellular pH and tension during ischemia in the isolated rabbit ventricle. *Am J Physiol* 1984; 247:H916–27.

14 Jacobus WE, Pores IH, Lucas SK, Clayton HK, Weisfeldt ML, Flaherty TJ. The role of intracellular pH in the control of normal and ischaemic myocardial contractility: a ^{31}P nuclear magnetic resonance and mass spectrometry study. In: Nuccitelli R, Deamer DW, eds. *Intracellular pH: its measurement, regulation and utilisation in cellular functions.* New York: Alan R Liss, 1982:537–65.

15 Allen DG, Morris PG, Orchard CH, Pirolo JS. A nuclear magnetic resonance study of metabolism in the ferret heart during hypoxia and inhibition of glycolysis. *J Physiol (Lond)* 1985;361:185–204.

16 Gebert G, Benzing H, Strohm M. Changes in the interstitial pH of dog myocardium in response to local ischemia, hypoxia, hyper- and hypo-capnia, measured continuously by means of glass microelectrodes. *Pflugers Arch* 1971;339:72–81.

17 Cobbe SM, Poole-Wilson PA. Catheter tip pH electrodes for continuous intravascular recording. *J Med Eng Technol* 1980;4:122–4.

18 Webb SC, Rickards AF, Poole-Wilson PA. Coronary sinus potassium concentration recorded during coronary angioplasty. *Br Heart J* 1983;50:146–8.

19 Cobbe SM, Parker DJ, Poole-Wilson PA. Tissue and coronary venous pH in ischaemic canine myocardium. *Clin Cardiol* 1982;5:153–6.

20 Serruys PW, Wijns W, van den Brand M, *et al.* Left ventricular performance, regional blood flow, wall motion and lactate metabolism during transluminal angioplasty. *Circulation* 1984;70:25–36.

21 Cobbe SM, Poole-Wilson PA. Continuous coronary sinus and arterial pH monitoring during pacing-induced ischaemia in coronary artery disease. *Br Heart J* 1982;47:369–74.

22 Jennings RB, Kaltenbach JP, Sommers HM, Bahr GF, Wartman WB. Studies of the dying myocardial cell. In: James TN, Keyes JW, eds. *The aetiology of myocardial infarction.* London: J and A Churchill, 1963:189–205.

23 Serruys PW, van den Brand M, Brower RW, Hugenholtz PG. Regional cardioplegia and cardioprotection during transluminal angioplasty, which role for nifedipine? *Eur Heart J* 1983;4(suppl C):115–21.

24 Donaldson RM, Taggart P, Swanton H, Fox K, Noble D, Rickards AF. Intracardiac electrode detection of early ischaemia in man. *Br Heart J* 1983;50:213–21.

25 Neely JR, Rovetto MJ, Whitmer JT, Morgan HE. Effects of ischemia on function and metabolism of the isolated working rat heart. *Am J Physiol* 1973; 225:651–8.

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Observations on the warm up phenomenon in angina pectoris

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SUMMARY Adaptation to exercise was investigated in 14 men aged 34–69 years (mean 51) with stable exertional angina caused by occlusive coronary artery disease. All underwent exercise electrocardiography to symptom limitation according to the Bruce protocol (first effort), and exercise to the onset of angina (warm up) followed by four minutes' rest, followed by exercise to symptom limitation (second effort). This protocol was repeated after sequential treatment for one month each with nifedipine 10 mg three times a day and with timolol 10 mg twice a day. Warm up significantly increased walking time to the onset of angina by 34·5% and to maximal exercise by 29·5%. The heart rate and rate-pressure product were significantly higher on second effort both at the onset of angina (by 7·0% and 11·1% respectively) and at maximal exercise (by 10·5% and 15·4% respectively). ST segment displacement was not significantly different after warm up. The effect of warm up on walking time to the onset of angina was markedly reduced after treatment with nifedipine but little influenced by timolol. Mean (SE) walking time after warm up on no treatment was 10·1 (0·7) min; after treatment with nifedipine it was 10·0 (0·6) min and after treatment with timolol it was 9·7 (0·4) min.

These data demonstrate a substantial improvement in exercise performance after warm up and are consistent with the hypothesis that submaximal exercise in angina pectoris facilitates myocardial oxygen uptake by coronary vasodilatation.

Heberden first described the loss of symptoms with continued exercise in a patient experiencing angina.[2] It has been variously described; by Osler as "walking through"[3] and by Wenckebach as the "second wind".[4] Gallavardin recorded the "warming up" effect of previous exercise in angina pectoris[5] and Price described the phenomenon as "first effort angina".[6] Gallavardin claimed it was not an uncommon phenomenon[5] but others have been unable to demonstrate it.[7] Wayne and Gaybriel described two patients whose exercise performance was enhanced when they re-exercised between five and 30 minutes after an attack of angina, the effect being lost when the interval was one hour.[8] Exercise performance was reduced when the patient re-exercised within two minutes of having symptoms.

Although the effects of physical training on exercise performance in angina pectoris have received attention[9 10] studies of short term adaptation to exercise are limited.[8 11 12]

Patients and methods

PATIENTS

We studied 14 white men aged 34–68 (mean 51) with a $\geqslant 6$ month history of stable exertional angina. All were normotensive (blood pressure $< 160/95$ mm Hg), and had no past history of myocardial infarction and no evidence of valvar heart disease. They also had a normal chest radiograph and resting electrocardiograph, but planar or downsloping ST segment depression of $\geqslant 1$ mm developed when they exercised according to the Bruce treadmill protocol. In all of them characteristic defects of thallium-201 myocardial imaging developed during exercise and coronary artery disease

A preliminary report of this work was presented to the Third Joint Meeting of the Working Groups of the European Society of Cardiology, Spa, Belgium 1983.[1]

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was confirmed by arteriography. Informed signed consent was obtained from all participants. The investigation had the approval of the hospital ethics committee.

METHODS

All patients performed the following tests on different days in random order while on no treatment (the Bruce treadmill protocol was used): (*a*) maximal exercise electrocardiography (first effort); (*b*) exercise to the onset of angina (warm up) followed by four minutes' rest followed by maximal exercise (second effort). The walking time to the onset of angina and to maximal exercise were recorded, together with heart rate (from the electrocardiograph) and systolic blood pressure (obtained with a sphygmomanometer).

After an interval of 2–4 weeks all patients were randomised into one of two groups; the first was treated with timolol 10 mg twice a day and the second with nifedipine 10 mg three times a day. The two exercise protocols were repeated after four weeks and the patients crossed over; the protocol was repeated at the end of a further four weeks. Nifedipine was given 30 minutes before exercise and timolol 60 minutes beforehand. Patients could take sublingual glyceryl trinitrate for symptomatic relief during the period of the study but not on the day of investigation. No other medication was taken. All recordings were made at the same time of day to exclude any possible circadian influence.[13] The mean (SD) temperature of the exercise laboratory was maintained at 20 (1)°C.

Exercise electrocardiography was performed on an Avionics A10 treadmill in conjunction with an Avionics 3000 three channel oscillographic monitor. Leads CM4, CM5, and CM6 were recorded for 5–10 seconds at rest, after each minute of exercise, at the end of exercise, and for each of 10 minutes of recovery. The treadmill and chart speeds were regularly checked and the recording apparatus was optimally damped. ST segment displacement 60 ms after the nadir of the S wave was computed and checked against the chart; the lead showing the greatest displacement at maximal exercise was chosen. We calculated the product of heart rate and systolic blood pressure.

We calculated the means and standard errors of the paired observations (on first and second efforts) and tested their difference from zero by Student's paired *t* test.

Results

All 14 men had important coronary artery disease (defined as a stenosis > 50% in the left main artery or > 70% in other major arteries). Ten subsequently underwent coronary artery bypass grafting. Left ventricular end diastolic pressure was normal in all but three in whom it was slightly raised (< 18 mm Hg). Regional hypokinesis was commonly found on left ventricular angiography but none of the patients showed more severe wall motion abnormalities.

PATIENTS NOT ON DRUG TREATMENT

Figs 1 and 2 show the mean walking times and the effect of warm up both on the onset of angina and maximal exercise. Walking time to the onset of angina was improved by 34·5% (p < 0·001) and to maximal exercise by 29·5% (p < 0·001). Figs 3 and 4 show the effect of warm up on the heart rate at the onset of angina and at maximal exercise. After warm up the heart rate at the onset of angina was increased by 7·0% (p < 0·01) and at maximal exercise by 10·5% (p < 0·01). Similarly, the rate-pressure product at the onset of angina and at maximal exercise was improved after warm up by 11·1% (p < 0·01) and 15·4% (p < 0·02) respectively (figs 5 and 6). ST segment displacements were not significantly different at the onset of angina before and after warm up (p > 0·05) or at maximal exercise before and after warm up (p > 0·05). There was no significant difference between the heart rate or rate-pressure product at the onset of angina on first effort and at the same walking time on second effort (p > 0·47, p > 0·15) (figs 7 and 8). In contrast, both the heart rate and rate-pressure product were higher (p < 0·025; p < 0·05) on second effort at the walking time of maximal exercise than on first effort (figs 7 and 8). ST segment depression was less on second

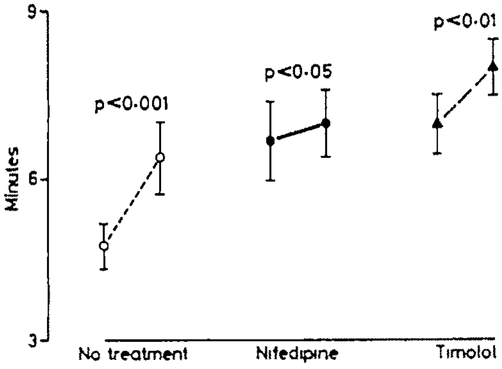

Fig 1 *Walking time to the onset of angina on first and second efforts (left and right hand data points respectively) on no treatment and after treatment for one month with nifedipine 10 mg three times a day and with timolol 10 mg twice a day. In this and subsequent figures the data points are group mean values and the vertical bars are 1 SE.*

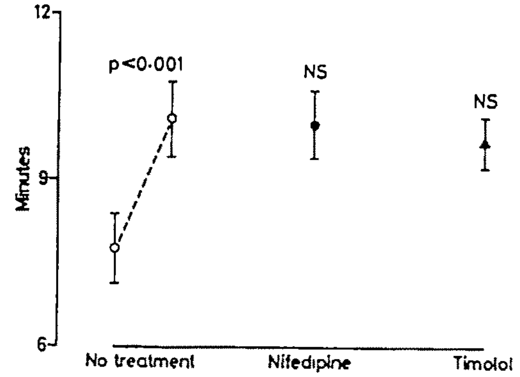

Fig 2 *Maximal walking time on first and second efforts on no treatment (left and right hand data points respectively) and on second effort after treatment with nifedipine and with timolol.*

effort both at the point of onset of angina and at the walking time of maximal exercise on first effort ($p < 0{\cdot}025$; $p < 0{\cdot}01$) (fig 9).

EFFECT OF NIFEDIPINE

Treatment with nifedipine increased the mean walking time to the onset of angina on first effort by 40·6% ($p < 0{\cdot}01$) (fig 1). Warm up increased the walking time to the onset of angina by a further 4·0% ($p < 0{\cdot}05$). The heart rate and rate-pressure product at the onset of angina increased by 2·4% and 4·0% respectively ($p < 0{\cdot}01$, $p < 0{\cdot}025$) (figs 3 and 5). On second effort, maximal walking time, heart rate, rate-pressure product, and ST segment depression did not differ significantly from values seen on no treatment after warm up ($p > 0{\cdot}40$, $p > 0{\cdot}15$, $p > 0{\cdot}15$, and $p > 0{\cdot}05$ respectively) (figs 2, 4, and 6).

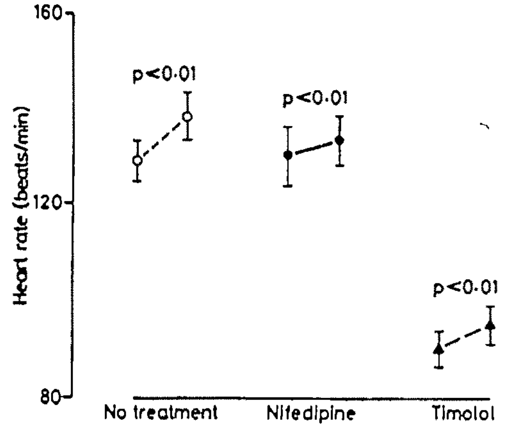

Fig 3 *Heart rate at the onset of angina on first and second efforts (left and right hand data points respectively) on no treatment and after treatment with nifedipine and with timolol.*

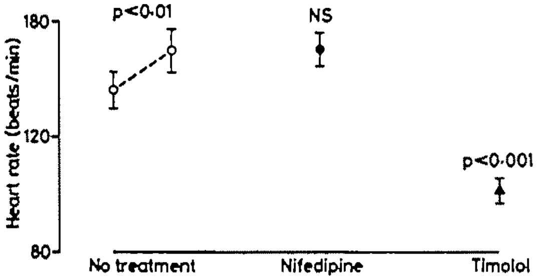

Fig 4 *Heart rate at maximal exercise on first and second efforts on no treatment (left and right hand data points respectively) and on second effort after treatment with nifedipine and with timolol.*

EFFECT OF TIMOLOL

As would be expected, timolol reduced the heart rate and rate-pressure product both on first and second efforts (figs 3 to 6). Treatment with timolol increased the walking time to the onset of angina on first effort by 46·9% ($p < 0{\cdot}001$) (fig 1). Warm up further increased the walking time to the onset of angina by 14·7% ($p < 0{\cdot}01$). The heart rate and rate-pressure product at the onset of angina were increased by 5·5% and 10·0% respectively on second effort ($p < 0{\cdot}01$; $p < 0{\cdot}005$) (figs 3 and 5). However, maximal walking time on second effort was not significantly different from that achieved on no treatment ($p > 0{\cdot}20$) (fig 2). On second effort the heart rate and rate-pressure product at maximal exercise were significantly lower on timolol than on no treatment ($p < 0{\cdot}001$; $p < 0{\cdot}001$) (figs 4 and 6). There was also less ST segment displacement than on no treatment ($p < 0{\cdot}01$) (fig 9).

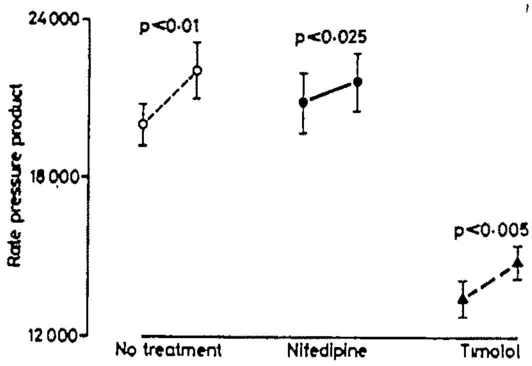

Fig 5 *Rate-pressure product (mm Hg × beats/min) at the onset of angina on first and second efforts (left and right hand data points respectively) on no treatment and after treatment with nifedipine and with timolol.*

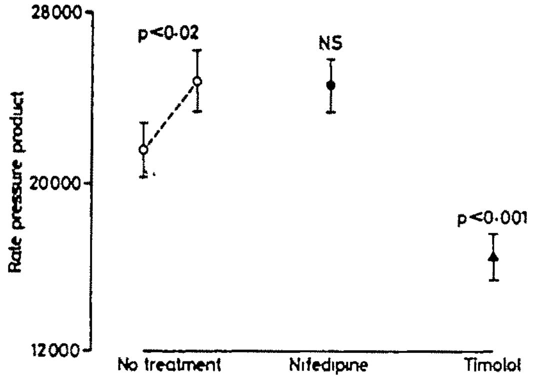

Fig 6 *Rate-pressure product (mm Hg × beats/min) at maximal exercise on first and second efforts on no treatment (left and right hand data points respectively) and on second effort after treatment with nifedipine and with timolol.*

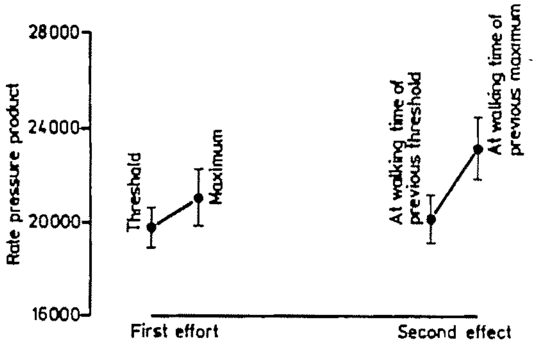

Fig 8 *The rate-pressure product (mm Hg × beats/min) on no treatment at the threshold for angina on first effort was similar to the product at the same walking time on second effort ($p > 0{\cdot}15$). On second effort the rate-pressure product at the maximum walking time achieved during the first effort was increased ($p < 0{\cdot}05$).*

Discussion

In previous studies of patients with stable exertional angina performance did not improve on repeated exercise testing after 10 to 15 minutes' recovery,[14–16] and a pause of 1–2 minutes also had no beneficial effect.[7] By contrast, in our subjects walking time was substantially improved when a first effort to the point of angina was followed by four minutes' recovery. Heart rates and rate-pressure products were also higher on second effort, suggesting increased myocardial oxygen consumption.[17] As the degree of ST segment depression was not significantly different, either at the point of angina or on maximal exercise before or after warm up, it may be inferred that the increase in heart work was not accompanied by increased myocardial ischaemia.[14] Coronary blood flow is closely related to myocardial oxygen demand[18] and coronary reserve is progressively diminished by stenosis of a major coronary vessel.[19] Slight variation in the calibre of a stenosed vessel has a major effect on blood flow[20] and may explain the variable exercise performance of patients with vasospastic angina.[21] A metabolically mediated vasodilatation of stenosed epicardial arteries could provide one explanation for our observations.

Nifedipine largely abolished the effect of warm up, and walking time to angina on second effort was increased by only 4%. Yet at maximal walking time, heart rate and rate-pressure product were not significantly different from those achieved without medication after warm up; the favourable action of

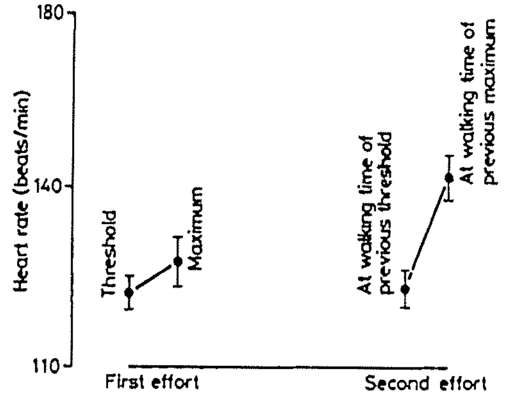

Fig 7 *The heart rate on no treatment at the threshold for angina at first effort was similar to the heart rate at the same walking time on second effort ($p > 0{\cdot}47$). The heart rate was significantly increased on second effort at the maximum walking time achieved during first effort ($p < 0{\cdot}025$).*

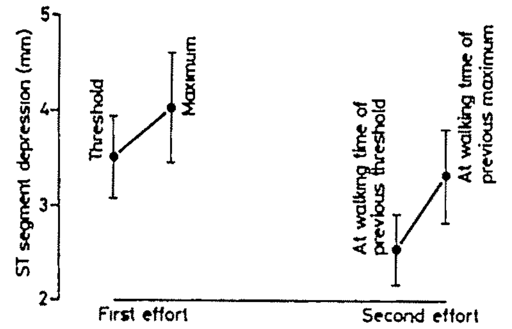

Fig 9 *ST segment depression (mm) on no treatment at the threshold for angina on first effort was greater than at the same walking time on second effort ($p < 0{\cdot}025$). ST segment depression at maximal exercise on first effort was also greater than that at the same walking time on second effort ($p < 0{\cdot}01$).*

nifedipine and the warm up effect may thus share a common mechanism. The pharmacodynamic effects of nifedipine are several and their net haemodynamic result is modified by peripheral circulatory reflex activity. Systemic administration of nifedipine at rest leads to a fall in total peripheral resistance and in coronary vascular resistance, with an increase in coronary blood flow. The reduction in afterload is to some extent buffered by reflex tachycardia and peripheral vasoconstriction.[22] Early exercise data suggested that nifedipine enhanced exercise capacity by a relative reduction in myocardial oxygen uptake (expressed by a lack of increase in the double product with increased performance) rather than by an increase (which would have been expressed by an increase in the double product).[23] After warm up, however, we found an increase in the double product in patients on nifedipine. Other investigators have suggested that the most important net effects include a decrease in coronary vascular resistance,[24] a reduction in the arteriocoronary sinus oxygen difference,[25] and an increase in coronary blood flow.[26] Nifedipine does not alter the filling pressure in normal left ventricular function.[27]

Reduction of myocardial oxygen demand is the major antianginal effect of β adrenoceptor blocking agents, including timolol.[28 29] As such agents may increase α mediated vasoconstriction of coronary vessels,[30] coronary vasodilatation, by whatever means, should enhance exercise performance. Our results accord with this: the warm up effect was not attenuated in subjects on timolol and walking time to the onset of angina on second effort was increased by 15%. Had a reduction in preload, afterload, or both been the explanation for the enhanced walking time in our patients after warm up, then the rate-pressure product (reflecting myocardial oxygen uptake) should not have increased significantly.

There has been some speculation about the possible mechanisms of the warm up effect.[6 31 32] There is a near constant rate-pressure product at the threshold of angina[14 33 34] and variation in symptoms may be accounted for by variation in the circulatory responses.[14] Robinson, however, did not observe a warm up effect, possibly because his protocol allowed 10 to 15 minutes' recovery between exercise trips.[14] Although we did not investigate this point systematically, it seems likely that the warm up effect is of short duration only. We chose a four minute recovery period for our protocol because it reflected the patients' experience.

Other determinants of myocardial oxygen consumption need to be considered in the context of the warm up effect. A reduction in wall tension due to reduced left ventricular end diastolic pressure caused by a fluid shift or vasodilatation may be a factor.[35] One study of supine bicycle exercise, however, demonstrated that although left ventricular end diastolic pressure was reduced during a second period of exercise 25 minutes after exercising to angina, mean values for exercise time, rate-pressure product, and ST segment depression at the onset of angina were not significantly different.[36] Our data do not exclude a contribution to the effect by this mechanism.

A recent study of patients with exertional angina who had isolated disease of the left anterior descending coronary artery showed that myocardial ischaemia was less during the second of two identical periods of pacing stress separated by 5–15 minutes.[37] Peak coronary flow, however, was not significantly different during the second period but regional myocardial oxygen consumption was reduced; the authors attributed this result to an ischaemic fall in contractility. Although this result does not support the suggestion that the warm up effect is due to coronary vasodilatation, it should be noted that their patients were not paced to a high rate-pressure product or to the same degree of ischaemia on the second occasion.

The warm up effect may be demonstrated objectively in the exercise laboratory, although its exact time course has yet to be defined. Our observations seem to favour coronary vasodilatation as the mechanism for this effect. It is not known whether a local metabolic, hormonal, or neurogenic pathway is responsible. The possibility of a contribution from a reflex reduction in afterload cannot, however, be discounted. Given the similarities between the warm up effect and treatment with nifedipine, it is noteworthy that nifedipine has been reported to be effective in relieving ischaemia only in myocardium supplied by a stenosed (but not occluded) vessel.[38] The relation between the warm up effect and coronary anatomy remains to be established.

References

1 Joy M, Cairns A, Shah S. Observations on the second wind phenomenon. *Eur Heart J* 1983;4 (suppl E):24.

2 Heberden W. A letter to Dr Heberden concerning the angina pectoris and an account of the dissection of one who had been troubled with that disorder. Medical Transactions published by the College of Physicians, London 1785;3:1–11.

3 Osler W. *Lectures on angina pectoris and allied states.* New York: D Appleton, 1897:52.

4 Wenckebach KF. Toter Punkt, second wind und angina pectoris. *Wien Klin Wochenschr* 1928;41:1–10.

5 Gallavardin L. *Les angines de poitrine.* Paris: Masson & Cie, 1925:119.

6 Price RK. First effort angina. Second wind in angina pectoris. *Br Heart J* 1951;13:197–202

7 Wayne EJ, LaPlace LB. Observations on angina of effort. *Clin Sci* 1933;**1**:103–29.

8 Wayne EJ, Gaybriel A. Observations on the effect of food, gastric distension, external temperature and repeated exercise on angina of effort with a note on angina sine dolore. *Clin Sci* 1934;**1**.287–304.

9 Detry JM, Bruce RA. Effects of physical training on exertional ST segment depression in coronary heart disease. *Circulation* 1971;**44**:390–7.

10 Sim DN, Neill WA. Investigation of the physiological basis for increased exercise threshold for angina pectoris after physical conditioning. *J Clin Invest* 1974;**54**:763–70.

11 Patterson JE, Clarke TW, Levy RL. A comparison of electrocardiographic changes observed during the anoxaemia test on normal persons and on patients with coronary sclerosis. *Am Heart J* 1942;**23**:837–46.

12 MacAlpin RN, Kattus AA. Adaptation to exercise in angina pectoris. The electrocardiogram during treadmill walking and coronary angiographic findings. *Circulation* 1966;**33**:183–201.

13 Joy M, Pollard CM, Nunan TO. Diurnal variation in exercise responses in angina pectoris. *Br Heart J* 1982;**48**:156–60.

14 Robinson BF. Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation* 1969;**35**:1073–83.

15 Redwood DR, Rosing DR, Goldstein RE, Beiser GD, Epstein SE. Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris. *Circulation* 1971;**43**:618–28.

16 Kattus AA, Alvaro AA, Zohman LR, Coulson AH. Comparison of placebo, nitroglycerin, and isosorbide dinitrate for effectiveness of relief of angina and duration of action. *Chest* 1979;**75**:17–23.

17 Gobel FL, Nordstrom LA, Nelson RR, Jorgensen CR, Wang Y. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation* 1978; **57**:549–56.

18 Feigl EO. Coronary physiology. *Physiol Rev* 1983; **63**:1–205.

19 Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol* 1974;**34**:48–55.

20 Epstein SE, Talbot TL. Dynamic coronary tone in precipitation, exacerbation and relief of angina pectoris. *Am J Cardiol* 1981;**48**:797–803.

21 DeServi S, Specchia G, Falcone C, *et al* Variable threshold exertional angina in patients with transient vasospastic myocardial ischaemia. Repeat exercise test results and therapeutic implications. *Am J Cardiol* 1983;**51**:397–402.

22 Stone PH, Antman EM, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II Haemodynamic effects and clinical applications. *Ann Intern Med* 1980; **93**:896–904.

23 Moskowitz RM, Piccini PA, Nacarell G, Zelis R. Nifedipine therapy for stable angina pectoris: preliminary results of effects on angina frequency and treadmill exercise response. *Am J Cardiol* 1979; **44**:811–6.

24 Bagger JP, Nielsen TT. Influence of nifedipine on coronary haemodynamics and myocardial metabolism in coronary disease. *Eur Heart J* 1985;**6**:75–84.

25 Stone D. The effects of nifedipine on coronary haemodynamics and exercise left ventricular function. *Postgrad Med J* 1983;**59** (suppl 2):25–38.

26 Specchia G, DeServi S, Falcone C, *et al.* Effects of nifedipine on coronary haemodynamic findings during exercise in patients with stable exertional angina. *Circulation* 1983;**68**.1035–43.

27 Kurnik PB, Tiefenbrunn AJ, Ludbrook PA. The dependence of the cardiac effects of nifedipine on the responses of the peripheral vascular system. *Circulation* 1984;**69**:963–72

28 Thadani U, Sharma B, Meeran MK, Majid PA, Whitaker W, Taylor SH. Comparison of adrenergic beta-receptor antagonists in angina pectoris. *Br Med J* 1973;**i**:138–42.

29 Harris FJ, Low RI, Paumer L, Amsterdam EA, Mason DT. Anti anginal efficacy and improved exercise performance with timolol. Twice-daily beta-blockade in ischaemic heart disease. *Am J Cardiol* 1983;**51**:13–8.

30 Kern MJ, Ganz P, Horowitz JD, *et al.* Potentiation of coronary vasoconstriction by beta adrenergic blockade. *Circulation* 1983;**67**:1178–85.

31 MacAlpin RN, Kattus AA. Adaptation of exercise in angina pectoris. The electrocardiogram during treadmill walking and coronary angiographic findings. *Circulation* 1966;**33**:183–201.

32 Jaffe MD, Quinn NK. Warm up phenomenon in angina pectoris. *Lancet* 1980;**ii**:934–6.

33 Fabián J, Stolz I, Janota M, Roháč J. Reproducibility of exercise tests in patients with symptomatic ischaemic heart disease. *Br Heart J* 1975,**37**:785–9

34 Starling MR, Moody M, Crawford MH, Levi B, O'Rourke RA. Repeat exercise treadmill testing: variability of results in patients with angina pectoris. *Am Heart J* 1984;**107**:298–303.

35 Rubenberg HL. Of pre-loads, after-loads and warm ups [Letter]. *Lancet* 1981;**i**:272.

36 Thadani U, Lewis JR, Manyai D, *et al* Are the clinical and haemodynamic events during exercise stress testing in invasive studies in patients with angina pectoris reproducible? *Circulation* 1980;**61**·744–50.

37 Williams DO, Bass TA, Gewirtz H, Most AS. Adaptation to the stress of tachycardia in patients with coronary artery disease. Insight into the mechanism of the warm-up phenomenon. *Circulation* 1985;**71**· 687–92.

38 Shulz W, Jost S, Kober G, Kaltenbach M. Relation of antianginal efficacy of nifedipine to degree of coronary arterial narrowing and to presence of coronary collateral vessels. *Am J Cardiol* 1985;**55**:26–32.

Br Heart J 1987;58:122–8

Felodipine in patients with chronic heart failure: discrepant haemodynamic and clinical effects

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SUMMARY Previous open studies have suggested that felodipine, a selective calcium antagonist and vasodilator, may be useful in the treatment of heart failure. A double blind placebo controlled crossover trial was therefore conducted to investigate the clinical and haemodynamic effects of felodipine in 15 patients with chronic ischaemic heart failure in New York Heart Association symptom class III. Felodipine significantly increased resting and exercise (25 W bicycle ergometry) cardiac output without producing concomitant changes in resting or exercise heart rate or right and left ventricular filling pressures. Felodipine did not significantly improve symptom scores or exercise capacity in the group as a whole. It also resulted in significant fluid retention as shown by a rise in ankle circumference, body weight, and a fall in haematocrit.

Further research is required to elucidate the mechanism that is responsible for the discrepancy between the haemodynamic and clinical effects of felodipine in patients with moderately severe heart failure.

The ability of peripheral vasodilators to improve cardiac performance in cardiac failure has been well documented.[1-3] This, together with the compelling theoretical reasons that support their use,[4-8] implies that vasodilators are now accepted as a viable treatment option in the management of heart failure. Some vasodilators have also been shown to improve the functional status[9-12] and prognosis[13] of patients with heart failure. The calcium antagonists as a class of vasodilator, however, have not been widely accepted as a treatment option in heart failure largely because of their negative inotropic effects.

Felodipine is a new calcium antagonist vasodilator with negligible negative inotropic properties.[14] It has been shown in open studies to produce beneficial haemodynamic effects[15-17] and improvements in the functional capacity of patients in congestive heart failure.[18] The aim of this study was to establish whether these preliminary results were borne out in a double blind placebo controlled crossover trial.

Patients and methods

PATIENT POPULATION

We studied 15 patients (11 men and four women, mean age 61 years, range 50–69). They all had chronic heart failure in New York Heart Association functional class III and documented coronary artery disease and were in stable sinus rhythm. At entry their maximum exercise capacity was not greater than 90 W on a bicycle ergometer; the exercise workload started at 10 W and increased by 10 W/min. The mean (SEM) maximum work performed was 12·6 (1·6) kJ (equivalent to 5 9 (0·4) minutes of exercise). Their limiting symptoms were dyspnoea, leg fatigue, or exhaustion. Mean (SEM) left ventricular ejection fraction as assessed by cross sectional echocardiography was 25 (3)%. Throughout the study period diuretics and digoxin were the only other agents used to treat heart failure and the average (SEM) dose of frusemide taken by the patients was 83 (14) mg per day. The doses of digoxin and diuretics were kept constant throughout the study.

STUDY DESIGN

This study was a double blind crossover comparison of the effects of felodipine and placebo after three weeks' treatment (fig 1). It consisted of a two week

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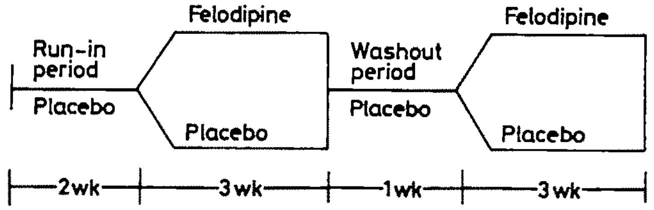

Clinical history and examination	X	X	X	X	X	X	X
Blood samples		X		X			X
Chest x-ray		X		X			X
Exercise test	XXX	X		X	X		X
Echocardiography	X	X		X	X		X
Invasive measurement of haemodynamic function				X			X

Fig 1 *Study protocol.*

single blind placebo run in period that started after the patient was deemed to be suitable on grounds of clinical assessments, echocardiography, and exercise testing as outlined above. At the end of this period the patient was admitted to hospital for basal clinical, echocardiographic, and exercise capacity assessments. The patient was then randomised to treatment with either felodipine or placebo. The dose aimed for was two tablets twice daily of felodipine (equivalent to 10 mg twice a day) or placebo, but if this was not tolerated lower doses were given. After three weeks' treatment the patient was readmitted for clinical and non-invasive investigations as before, but this time invasive haemodynamic assessment was also performed. On completion of this assessment the patient was given placebo tablets for one week. At the end of this period the patient was readmitted for the same clinical and non-invasive assessment before entry into the second phase of the randomised crossover trial. Finally, at the end of this second three week period the patient was again admitted for repeat clinical and haemodynamic evaluations. The assessments were performed at the same time of day and at the same time after tablet administration in each patient. All 15 patients completed the study protocol except for one patient who refused the second right heart catheterisation.

The protocol for this study was accepted by the United Kingdom Committee on Safety of Medicines under the Clinical Trial Exemption scheme. This study was also approved by the East Birmingham Hospital Ethical Subcommittee. Informed written consent was obtained from each patient.

PROCEDURES

Clinical assessments

At each visit the patient was asked to assess progress from the previous visit using a scale of 1 to 7 as an indication of subjective clinical score: (1) markedly worse, (2) moderately worse, (3) slightly worse, (4) unchanged, (5) slightly improved, (6) moderately improved, and (7) markedly improved. The baseline clinical score was taken to be 4, and at each subsequent visit the score increased or decreased in a cumulative fashion depending on the degree of changes from the previous visit. Any unwanted effects were recorded at the time of each clinical assessment. Ankle circumference, measured at 10 cm proximal to the medial maleolus, and body weight were also recorded at each visit.

Exercise tests

Maximal symptom limited exercise tests were performed on an upright bicycle ergometer by a protocol which started at 10 W and the workload was increased by 10 W/min. The patient's heart rate, blood pressure, and quantified symptom scores (dyspnoea, exhaustion, and/or muscle fatigue according to Borg's scale[19]) were recorded at the end of each workload.

Haemodynamic measurements

We used the electrocardiogram, thermodilution Swan-Ganz catheters, and arterial cannulas to measure the following haemodynamic variables: heart rate (HR); right atrial (RAP), pulmonary arterial (PAP), and wedge (PAWP) pressures; systemic arterial pressures (AP); and cardiac output (CO, measured in triplicate). Baseline resting haemodynamic data were obtained at least 20 minutes after insertion of the catheters. Two control readings were taken 15 minutes apart, and the haemodynamic state was considered to be stable only if the values differed by less than 10%.[20] No food or drink (except water) was given during the study period to avoid fluctuations in haemodynamic state of the patients.[21] The last dose of trial medication was taken at least 12 hours before the baseline haemodynamic measurements.

The trial medication was given after recording the resting data, and the haemodynamic response was recorded 30 to 90 minutes after ingestion. The patient was then transferred to a bicycle ergometer and the haemodynamic data were collected during exercise that started at 25 W for three minutes and increased in steps of 10 W every three minutes.

Data analysis

The following haemodynamic variables were calculated: cardiac index (CI = CO/body surface area in l/min/m^2); stroke volume index (SVI = CI/HR in

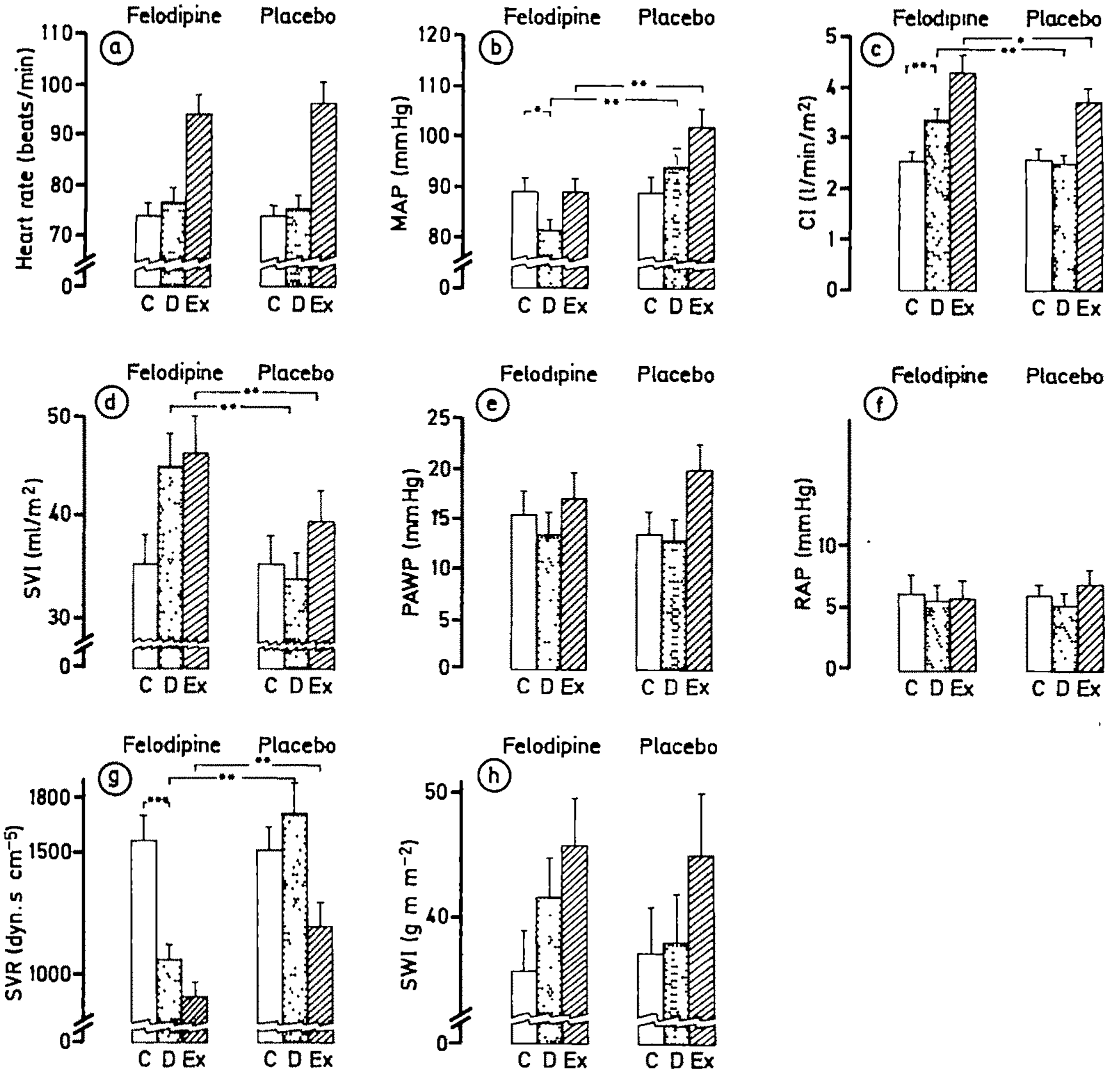

Fig 2 *Haemodynamic effects of felodipine versus placebo. (a) Heart rate, (b) MAP, mean systemic arterial pressure, (c) CI, cardiac index, (d) SVI, stroke volume index, (e) PAWP, pulmonary artery wedge pressure, (f) RAP, right atrial pressure, (g) SVR, systemic vascular resistance, (h) SWI, left ventricular stroke work index. C, control; D, after drug administration; Ex, during 25 W exercise. The bars denote SEM.* $*p < 0{\cdot}05$, $**p < 0{\cdot}01$, $***p < 0{\cdot}001$.

ml/m^2); left ventricular stroke work index (SWI = (MAP − PAWP) × SVI × 0·0136 g m/m^2); systemic vascular resistance (SVR = (MAP − RAP)/CO × 80 dyn s cm^{-5}).

We used the Wilcoxon matched-pair signed ranks test for statistical analysis. Differences were taken to be significant at $p < 0{\cdot}05$. All results are expressed as mean (SEM).

Results

RESTING AND EXERCISE HAEMODYNAMIC FUNCTION

The haemodynamic effects of felodipine and placebo are compared in fig 2 and table 1. The effect of felodipine on the heart rate was not significantly different from that of placebo, either at rest or during exercise at the same workload. The resting and exercise mean systemic arterial pressures were lower after felodipine than after placebo. The resting and exercise cardiac outputs were significantly greater with felodipine, and since there was no significant concomitant change in heart rate these increases were caused by felodipine induced increases in stroke volume. The pulmonary arterial wedge pressure and right atrial pressure were not significantly different after felodipine, either at rest or during exercise. The systemic vascular resistance was significantly lower after felodipine both at rest and during exercise.

CLINICAL DATA

The initial clinical score was taken to be 4 at the start of each treatment period. After the first week of treatment the score showed a tendency for symptoms to become worse on both placebo (3·73 (0·21)) and felodipine (3·53 (0·27)). After three weeks, however, the score reverted towards the control level on placebo treatment (3·93 (0·25)), but it tended to fall further on felodipine (3·27 (0·40)). This difference was not statistically significant.

The ankle circumference was significantly greater ($p < 0{\cdot}05$) during treatment with felodipine (23·0 (0·37) cm) than with placebo (22·3 (0·39) cm). The body weight was similarly increased ($p < 0{\cdot}05$) with felodipine (71·9 (3·0) kg *vs* placebo 70·9 (3·1) kg).

Table 1 *Effects of felodipine versus placebo*

Case No	℞	*PAWP*			*MAP*			*CI*			*SVI*			*Exercise* duration (min)*
		C	*D*	*Ex*	*C*	*D*	*Ex*	*C*	*D*	*Ex*	*C*	*D*	*Ex*	
1	P	22	15	21	93	93	100	2·8	2·8	3·5	33	30	33	6
	F	21	19	33	97	93	103	2·7	4·1	4·8	34	54	51	6
2	P	11	5	33	104	103	108	3·3	2·9	5·4	43	37	49	6·33
	F	10	8	19	92	88	96	3·1	4·1	6·0	41	51	58	8
3	P	15	8	12	73	80	80	2·4	1·9	3·2	33	26	37	4
	F	18	8	12	95	90	73	2·7	2·7	3·7	38	35	42	4·5
4	P	4	6	9	102	109	124	2·7	2·5	3·2	41	37	42	5
	F	12	13	11	102	92	92	2·8	3·8	4·4	40	50	54	3
5	P	9	11	21	94	89	110	2·6	2·5	5·1	38	35	64	9
	F	12	11	8	88	75	78	2·7	2·8	3·5	49	52	58	6
6	P	24	20	30	94	100	107	2·5	2·6	3·2	37	34	34	6
	F	32	23	24	89	72	90	2·4	3·3	4·0	33	47	41	6
7	P	6	7	9	97	132	124	2·9	2·2	3·8	45	37	40	4
	F	7	4	—	109	83	—	2·2	3·3	—	33	47	—	4
8	P	30	28	31	96	96	114	1·6	2·0	2·6	25	29	33	7
	F	32	28	31	98	89	101	1·6	2·4	2·7	24	35	35	5
9	P	15	18	17	83	93	96	4·7	4·7	6·1	65	65	66	7
	F	16	14	12	82	71	82	4·8	5·6	7·4	63	75	76	7
10	P	8	6	13	79	80	98	1·8	2·4	3·4	27	35	37	9
	F	(refused repeat right heart catheterisation)												9·33
11	P	9	11	14	100	99	98	2·4	2·4	3·7	34	36	44	6
	F	6	7	15	82	76	103	2·0	3·5	4·3	32	50	46	6·5
12	P	5	6	7	94	98	97	2·8	2·6	3·2	33	30	30	7
	F	2	5	4	80	75	87	2·2	3·6	3·2	26	39	31	8·17
13	P	12	10	8	81	84	86	2·0	2·0	3·1	25	25	32	8
	F	8	6	8	83	77	83	2·0	2·8	3·7	24	28	37	7·17
14	P	8	9	19	80	81	108	2·4	2·5	3·9	32	33	28	7
	F	12	12	14	79	83	89	2·7	3·0	5·5	38	41	48	7
15	P	26	32	33	66	73	83	2·0	1·8	2·5	22	20	25	9
	F	27	31	32	73	79	83	2·0	2·4	2·9	21	26	27	9
Mean	P	13·6	12·8	19·8	89·1	94·0	102·2	2·6	2·5	3·7	35·4	33·8	39·6	6·7
(SEM)		2·1	2·1	2·8	2·9	3·8	3·4	0·2	0·2	0·3	2·7	2·6	3·1	0·4
Mean	F	15·4	13·5	17·1	89·2	81·6	89·2	2·6	3·4	4·3	35·3	44·9	46·3	6·4
(SEM)		2·5	2·2	2·5	2·6	2·0	2·5	0·2	0·2	0·4	3·0	3·3	3·7	0·5

C, control at rest; CI, cardiac index; D, after drug administration at rest; F, felodipine; MAP, mean arterial pressure; P, placebo: PAWP, pulmonary artery wedge pressure; SVI, stroke volume index.

*Symptom limited exercise duration without invasive monitoring.

Table 2 *Unwanted effects experienced by patients in a double blind crossover trial of felodipine and placebo*

Symptoms	*Felodipine*	*Placebo*
Headache	8	5
Palpitation	3	2
Flushing	4	1
Faintness/dizziness	6	5
Peripheral oedema	6	3
Increased angina	5	3
Tiredness	8	7
Sedation	5	6
Insomnia	7	6
Depression	3	0
Nausea	5	5
Heartburn	1	3
Indigestion	0	2
Flatulence	3	1
Constipation	5	3
Rash	0	1
Increased dyspnoea	6	7
Wheezing	1	2

Table 2 shows the unwanted effects reported by the patients. Apart from symptoms related to vasodilation, felodipine did not appear to cause any more unwanted effects than placebo. Three patients had to have the dose of the study drug reduced because of unwanted effects when they were taking felodipine. None of the patients on placebo needed a reduction in the dose.

EXERCISE TOLERANCE TESTS

On entry into the study 12 patients had dyspnoea, one had leg fatigue, and in two both symptoms limited exercise. During the double blind study periods there was a tendency for more patients to have leg fatigue as a limiting symptom on felodipine (nine patients) than on placebo at different stages of the protocol (5–6 patients). There was no difference in the frequency of dyspnoea (10–11 patients on each treatment).

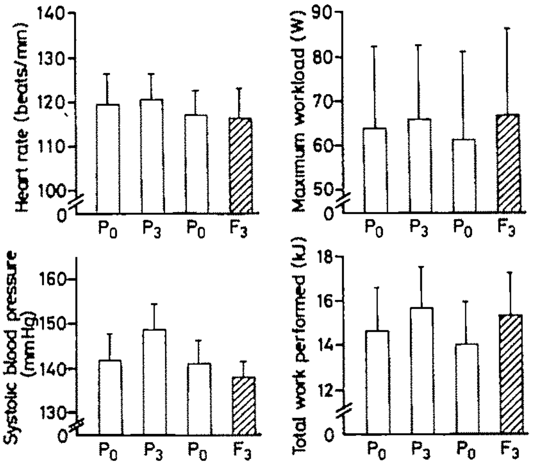

Fig 3 *Maximal exercise test results for patients during treatment with felodipine or placebo: maximum heart rate, and systolic blood pressure at end of exercise, maximum workload, total work performed. Bars denote SEM. P_0, at the beginning of either treatment period; P_3, after three weeks of placebo; and F_3, after three weeks of felodipine.*

Figure 3 shows the workload achieved and the heart rate and blood pressure at the end of symptom limited exercise. There was no significant difference in the highest workload achieved and the total work performed between patients on felodipine and on placebo. The heart rate and blood pressure at the end of exercise were also similar on felodipine and placebo. The exercise capacity at various stages during the trial when the patients were taking placebo showed no significant training effect.

HAEMATOLOGICAL AND BIOCHEMICAL RESULTS

Most standard haematological or biochemical indices did not change significantly during either of the treatment periods; however, serum potassium (3·9 (0·12) *vs* 4·2 (0·12) mmol/l, $p < 0·05$), the haematocrit (41·5 (0·9)% *vs* 43·5 (0·8)%, $p < 0·05$), and the erythrocyte count (4·59 (0·13) 4·81 (0·11) × 10^{12}/l, $p < 0·05$) fell while patients were taking felodipine. The results shown are those at the end of three weeks on felodipine and at the end of three weeks on placebo.

CHEST RADIOGRAPHY

The cardiothoracic ratio and the size of the cardiac silhouette did not change during either of the treatment periods.

Discussion

Unlike previous studies which suggested that felodipine can produce favourable effects in heart failure[15–18] our study did not show that this agent improved the symptoms and exercise capacity of a group of patients with chronic heart failure, despite its ability to produce desirable haemodynamic effects (as reflected by the increased cardiac index at rest and during exercise). Felodipine had considerable undesirable effects in our patients. Ankle circumference, body weight, and the fall in haematocrit showed that they retained more fluid during treatment with felodipine than with placebo.

When Emanuelsson *et al* studied the short term haemodynamic effects of felodipine they reported a significant decrease in heart rate and pulmonary capillary wedge pressure from baseline to post-felodipine period.[15] In a similar group of patients Timmis *et al* found no decrease in heart rate, but there was a large fall in pulmonary wedge pressure.[16] When we used comparable doses of felodipine (5–10 mg) in a double blind study we found no significant change in either heart rate or pulmonary artery wedge pressure between baseline and post-felodipine values and between placebo and felodipine treatment. It is impossible to state whether these differences were caused by dissimilarity in patient populations studied or observer bias.

The disparity between the results obtained in this double blind study and those obtained previously in open studies underlines the importance of controlled randomised trials. This is particularly true when obtaining subjective data, such as symptoms and exercise capacity. In another open study, Timmis and colleagues reported that the exercise capacity of their patients with heart failure was improved by felodipine,[18] but this was not confirmed by the results of our double blind study. They attributed the felodipine induced increase in exercise capacity to the attenuation of the rise in left ventricular filling pressure during exercise. However, when we identified the subgroup of patients whose left ventricular filling pressure during submaximal exercise (25 W) was lower with felodipine (16·4 (3·64) mm Hg *vs* 25·7 (4·23) mm Hg with placebo) we found that felodipine did not increase their exercise capacity (18·56 (2·03) kJ on felodipine *vs* 18·13 (2·09) kJ on placebo). Our result is consistent with the findings of other investigators who studied other arteriolar dilators, for example hydralazine and minoxidil, in randomised studies[22 23] where beneficial effects on haemodynamic criteria were not translated to clinical improvements.

Why did the haemodynamic findings appear to be discrepant with the clinical outcome and results of exercise test? There are several possible explanations. The study may not have been long enough. However, the unwanted effects of felodipine in certain patients, such as fluid retention, might have become worse if the study had been prolonged. Furthermore, previous studies have shown that short term haemodynamic effects of vasodilators do not, in general, correlate with long term clinical response.[24] Hence, the longer the treatment period, the less likely was the haemodynamic assessment to be able to predict the clinical outcome. Alternatively, the study may have been too long and tolerance may be responsible for the discrepancy. This is unlikely because the haemodynamic effects have been shown to be sustained even after a longer period of treatment.[18] The dosages used may not be high enough. This is also unlikely because considerable vasodilation was observed after the administration of felodipine at the dosages given, and higher doses would be associated with worse side effects.

It may be that the wrong type of patients were studied. In conducting this study, we took great care to study a homogeneous population of patients with heart failure—they all had New York Heart Association class III heart failure caused by coronary artery disease with a left ventricular ejection fraction of 25 (3)% and exercise capacity of 12·6 (1·6) kJ. But patients in heart failure are still likely to be very heterogeneous, and various factors, including valve dysfunction, rhythm or conduction abnormalities, ventricular aneurysms, inhomogeneous myocardial contraction, triggering of hormonal compensatory mechanisms, and varied response to drug treatment would contribute to the heterogeneity. The group as a whole may not show a positive clinical response to felodipine and this may be because the proportion of patients who showed beneficial effects did not exceed those who showed deterioration. Nevertheless, in this study those who had enhanced exercise capacity with felodipine had similar felodipine induced increases in cardiac output and left ventricular stroke work as those in whom exercise capacity was reduced. It may be that such drug induced increases in cardiac output and left ventricular stroke work do not necessarily lead to drug related improvements in clinical status and exercise capacity.

There is as yet no satisfactory explanation for the discrepancy between haemodynamic data and clinical findings. It is crucial to resolve this discrepancy because drug development is in part dependent on objective data obtained from haemodynamic measurements. If the results from haemodynamic evaluation cannot be related to the clinical effects of drugs, then alternative methods of assessment will have to be found, especially for the initial phases of drug development. However, before adopting this approach and rather than abandoning the practice of haemodynamic evaluation of the efficacy of vasodilator treatment, as has been suggested by Franciosa *et al*,[25] we must carefully reconsider how to interpret haemodynamic data. More research is required to resolve the reported discrepancy.

We thank Mrs Elsie Gale and her team of technicians who helped to conduct this study. We thank Astra Clinical Research Unit, Edinburgh, for their generous financial support and help in data analysis, and AB Hassle, Molndal, Sweden, for supplying the felodipine tablets.

References

1 Chatterjee K, Drew D, Parmley WW, Klausner SC, Polansky J, Zacherle B. Combination vasodilator therapy for severe chronic heart failure. *Ann Intern Med* 1976;85:467–70.

2 Franciosa JA, Pierpont G, Cohn JN. Hemodynamic improvement after oral hydralazine in left ventricular failure. *Ann Intern Med* 1977;86:388–93.

3 Massie B, Ports T, Chatterjee K, *et al.* Long-term vasodilator therapy for heart failure: clinical response and its relationship to hemodynamic measurements. *Circulation* 1981;63:269–78.

4 Chatterjee K. Vasodilator therapy for heart failure. *Ann Intern Med* 1975;83:421–3.

5 Chatterjee K, Parmley WW. The role of vasodilator therapy in heart failure. *Prog Cardiovasc Dis* 1976;19:301–25.

6 Cohn JN, Franciosa JA. Vasodilator therapy of cardiac failure. *N Engl J Med* 1977;297:27–31, 254–8.

7 Braunwald E. Vasodilator therapy—a physiologic approach to the treatment of heart failure. *N Engl J Med* 1977;297:331–3.

8 Mason DT. Afterload reduction and cardiac performance. Physiologic basis of systemic vasodilators as a new approach in treatment of congestive heart failure. *Am J Med* 1978;65:106–25.

9 Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic heart failure. *J Am Coll Cardiol* 1983;2:755–63.

10 Sharpe DN, Murphy J, Coxen P, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. *Circulation* 1984;70:271–8.

11 Leier CV, Huss P, Magorien RD, Unverferth DV. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy in congestive heart failure. *Circulation* 1983;67:817–22.

12 Cleland JGF, Dargie HJ, Ball SG, *et al.* Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. *Br Heart J* 1985; 54:305–12.

13 Cohn JN, Archibald DG, Ziesche S, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veteran Administration cooperative study. *N Engl J Med* 1986; 314:1547–52.

14 Ljung B. Vascular selectivity of felodipine. *Drugs* 1985;29(suppl 2):46–58.

15 Emanuelsson H, Hjalmarson A, Holmberg S, Waagstein F. Acute haemodynamic effects of felodipine in congestive heart failure. *Eur J Clin Pharmacol* 1985;28:489–93.

16 Timmis AD, Campbell S, Monaghan MJ, Walker L, Jewitt DE. Acute haemodynamic and metabolic effects of felodipine in congestive heart failure. *Br Heart J* 1984;51:445–51.

17 Tweddel AC, Hutton I. Felodipine in ventricular dysfunction. *Eur Heart J* 1986;7:54–60.

18 Timmis AD, Smyth P, Kenny JF, Campbell S, Jewitt DE. Effects of vasodilator treatment with felodipine on haemodynamic responses to treadmill exercise in congestive heart failure. *Br Heart J* 1984;52:314–20.

19 Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;2:92–8.

20 McKay CR, Nana M, Kawanishi DT, *et al.* Importance of internal controls, statistical methods, and side effects in short-term trials of vasodilators: a study of hydralazine kinetics in patients with aortic regurgitation. *Circulation* 1985;72:865–72.

21 Cornyn JW, Massie BM, Unverfeth DV, Leier CV. Haemodynamic changes after meals and placebo treatment in chronic congestive heart failure. *Am J Cardiol* 1986;57:238–41.

22 Franciosa JA, Weber KT, Levine TB, *et al.* Hydralazine in the long-term treatment of chronic heart failure: lack of difference from placebo. *Am Heart J* 1982;104:587–94.

23 Franciosa JA, Jordan RA, Wilen MM, Leddy CL. Minoxidil in patients with chronic left heart failure: contrasting hemodynamic and clinical effects in a controlled trial. *Circulation* 1984;70:63–8.

24 Massie BM, Kramer BL, Topic N. Lack of relationship between the short-term hemodynamic effects of captopril and subsequent clinical response. *Circulation* 1984;69:1135–41.

25 Franciosa JA, Dunhman WB, Leddy CL. Hemodynamic effects of vasodilators and long-term response in heart failure. *J Am Coll Cardiol* 1984;3:1521–30.

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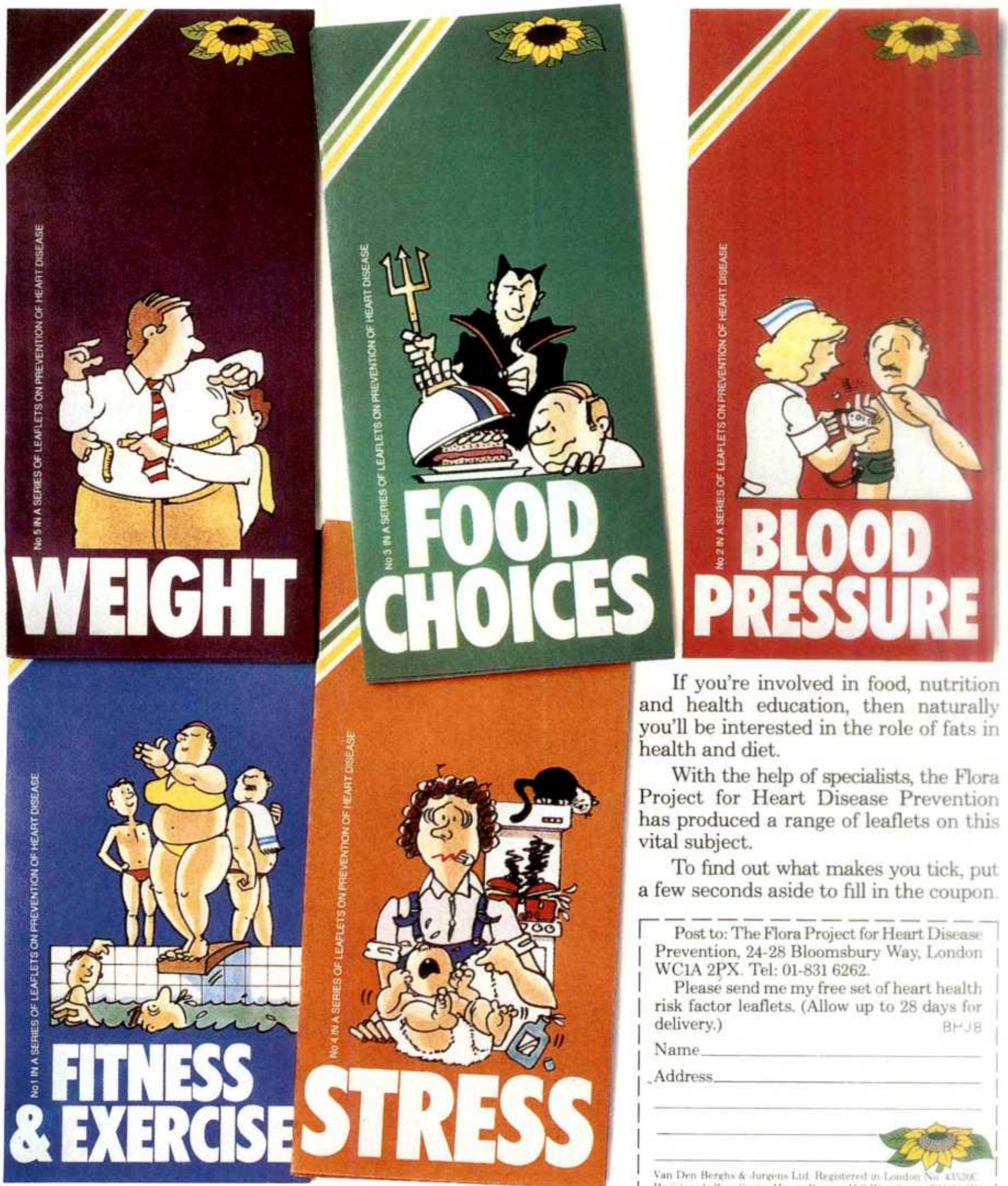
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Respiratory modulation of cardiac time intervals

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SUMMARY To determine the effect of respiration on systolic and diastolic time intervals, simultaneous phonocardiograms, carotid pulse tracings, M mode echocardiograms, and respiratory curve tracings were measured in 25 healthy subjects. The positioning of each cardiac cycle in relation to the phase of respiration was assessed and the dependency of heart rate and cardiac time intervals on respiration was examined. Heart rate clearly varied over the respiratory cycle. Where necessary the time intervals were corrected for heart rate or RR interval. The systolic time intervals showed a stronger dependency on respiratory group than the diastolic time intervals. The decrease in left ventricular ejection time and increase in pre-ejection period and isovolumic contraction time during inspiration support the idea that a relative increase in afterload in inspiration determines left ventricular systolic function. Isovolumic relaxation time also showed cyclic behaviour whereas the left ventricular filling time was affected by inspiration only. Filling time increased significantly when there was a transition from expiration to inspiration during left ventricular ejection. It seems that when isovolumic contraction takes place in expiration the diastolic intervals of this cycle take on an expiratory character. The increase in filling can be viewed as a compensatory effect that partly offsets the loss of stroke volume during inspiration.

The stroke volume of the left ventricle decreases during normal inspiration. This decrease is reflected in changes in left ventricular systolic time intervals: studies with normal subjects and various groups of patients have shown an increase in the pre-ejection period and a simultaneous decrease in left ventricular ejection time during inspiration.[1-3]

The mechanisms proposed to explain the drop in systolic efficiency postulate a drop in left ventricular filling owing to a phase lag between increased right and left ventricular output,[4 5] a decreased pulmonary venous return caused by pooling of the blood in the pulmonary vascular bed,[6] or a leftward septal shift caused by increased right ventricular filling.[7 8] More recently it has been suggested that the drop in pleural pressure during inspiration results in a relative increase in aortic[9-11] or atmospheric[12] pressure with respect to the left intraventricular pressure—this is equivalent to increasing the effective left ventricular afterload.

To obtain a clearer understanding of the mechanisms of the effects of respiration on the temporal events of the cardiac cycle we studied the changes of both the systolic and diastolic time intervals during the respiratory cycle in 25 healthy subjects. We aimed to study the temporal events more closely than before and, in the light of the increasing interest in diastolic function, to measure not only systolic but all cardiac time intervals.

Subjects and methods

We studied 20 men and five women (aged 20–36) with no clinical evidence or history of cardiac or pulmonary disease. We used a Hewlett Packard 77020A Ultrasound Imaging System with a paper speed of 100 mm/s to obtain the following strip chart recordings in each subject: electrocardiogram, phonocardiogram, carotid pulse tracing, M mode echocardiogram of the mitral valve, and respiratory curve (thermistor sensor) (fig 1). The subjects were given no instructions about breathing behaviour. While the subject was seated we recorded 50 consecutive heart beats. The following time intervals were mea-

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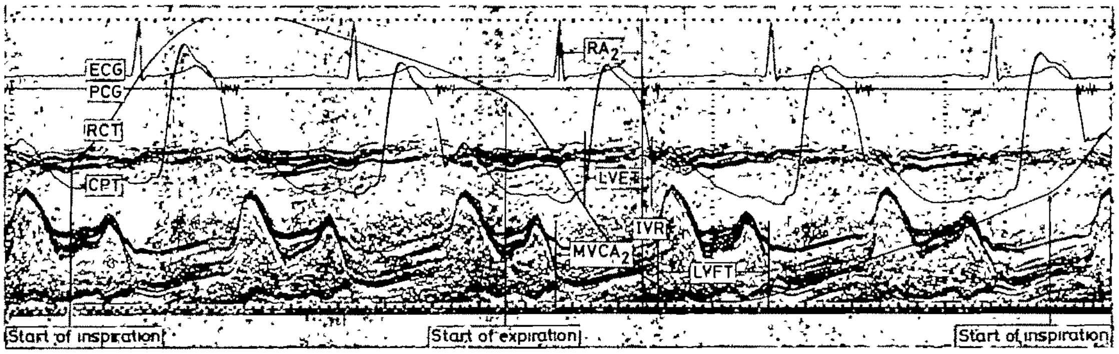

Fig 1 *Representative recording of mitral valve echocardiogram, electrocardiogram (ECG), phonocardiogram (PCG), respiratory curve tracing (RCT), and carotid pulse tracing (CPT). RA_2, time from R wave to second heart sound; LVET, left ventricular ejection time; IVR, isovolumic relaxation time; $MVCA_2$, time from mitral valve closure to second heart sound; LVFT, left ventricular filling time.*

sured to the nearest 5 ms: (*a*) RR interval; (*b*) left ventricular ejection time (LVET) from the onset of the rapid upstroke of the carotid pulse to the incisura; (*c*) isovolumic relaxation time (IVR) from the first high frequency vibration of the aortic component of the second heart sound (A_2) to the onset of mitral valve opening; (*d*) left ventricular filling time (LVFT) from the onset of mitral valve opening to mitral valve leaflet coaptation; (*e*) total electromechanical systole (RA_2) from the R wave of the electrocardiogram to A_2; (*f*) the interval from mitral valve closure of the preceding beat to A_2 ($MVCA_2$). Two time intervals were derived: (*a*) pre-ejection period (PEP) as RA_2–LVET and (*b*) isovolumic contraction time (IVC) as $MVCA_2$–LVET.

We used the respiratory curve to determine the start of inspiration and expiration. From this information we calculated the position of each heart beat in relation to the respiratory phase. The cardiac time intervals of each beat were assigned to one of eight groups according to the following criteria (fig 2):

Group 1—systole in the first half of inspiration.
Group 2—diastole in the second half of inspiration.
Group 3—transition from inspiration to expiration in diastole.
Group 4—transition from inspiration to expiration in systole.
Group 5—systole in the first half of expiration.
Group 6—diastole in the second half of expiration.
Group 7—transition from expiration to inspiration in diastole.
Group 8—transition from expiration to inspiration in systole.

Systole was defined as electromechanical systole (pre-ejection period and left ventricular ejection time) and diastole as the interval from aortic valve closure to mitral valve closure (isovolumic relaxation

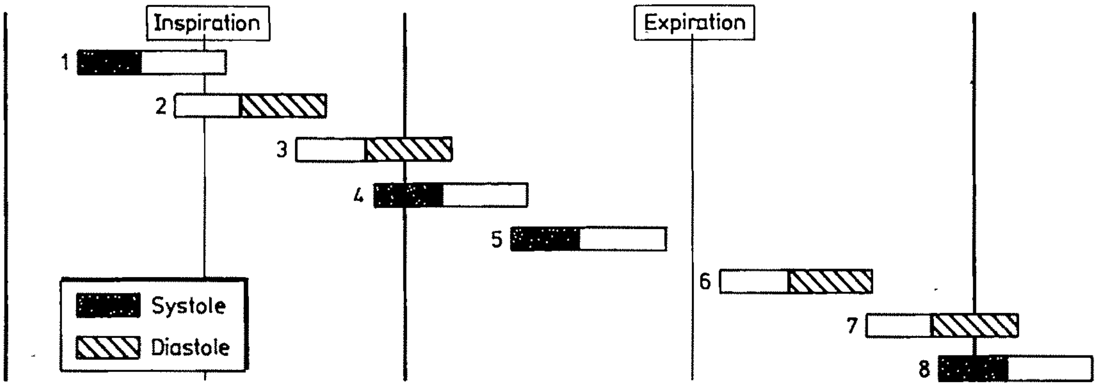

Fig 2 *Assignment of heart beats to one of eight respiratory groups (see text).*

time and left ventricular filling time).

Each of the above groups defines a particular coupling of the respiratory and cardiac rhythms. The group notation 1 to 8 does not represent the natural time course of respiration.

STATISTICAL ANALYSIS

The dependency of heart rate and the various cardiac time intervals on the respiratory group was determined by analysis of variance. Linear regression analysis was used to determine the dependency of the cardiac time intervals on heart rate and RR interval. Student's t test was used to determine the statistical significance of differences in intervals between consecutive cardiac cycles.

Results

The mean (SD) number of beats analysed per subject was 47 (4·8) and the mean number of respiratory cycles was 9 (2·7). Because of the variation in heart rate caused by respiration ($p < 0{\cdot}0001$) we examined cardiac intervals for their dependency on heart rate and RR interval (table 1). Left ventricular ejection time and isovolumic relaxation time were more significantly associated with heart rate, and left ventricular filling time and isovolumic contraction time more with RR interval. In all further examinations of the results we corrected these variables for these associations.

Analysis of variance showed a significant difference between the groups for each interval (table 2). The difference was strongest for the systolic intervals ($p < 0{\cdot}0001$), strong for filling time ($p < 0{\cdot}01$), and slightly weaker for isovolumic relaxation ($p < 0{\cdot}05$). Fig 3 shows the values of each cardiac time interval in each of the eight respiratory groups.

PRE-EJECTION PERIOD

Pre-ejection periods were longest at the transition from inspiration to expiration (group 4) and shortest at mid-expiration (group 6). The pre-ejection values within the second half of expiration (group 6–8) were approximately the same and increased progressively depending on the timing in inspiration.

ISOVOLUMIC CONTRACTION TIME

The results for the isovolumic contraction time generally resembled those for the pre-ejection period. Values reached a maximum slightly sooner, towards the end of inspiration (group 3), and remained at that level into expiration (group 4). Although at mid-expiration isovolumic contraction time fell to low values resembling those in the pre-ejection

Table 1 *Linear regression of heart rate and RR interval against cardiac time intervals*

	Heart rate		*RR interval*	
Interval	*Regression*	*p*	*Regression*	*p*
PEP	−0 43 × HR + 115 29	0 133 NS	0 05 × RR + 42 49	0 111 NS
IVC	−0 70 × HR + 112 74	0 005	0 08 × RR − 4 06	0 004*
LVET	−0 93 × HR + 311 99	0 0001*	0·10 × RR + 161·41	0 0002
IVR	−0 82 × HR + 145·54	0 0004*	0 09 × RR + 12 90	0 0006
LVFT	−6 50 × HR + 905 69	0 0000 (t = −13 86)	0·73 × RR − 169 39	0 0000* (t = 16 35)

*Higher level of significance of the two regression equations (HR and RR) for each interval.
PEP, pre-ejection period, IVC, isovolumic contraction time; LVET, left ventricular ejection time; IVR, isovolumic relaxation time, LVFT, left ventricular filling time

Table 2 *Heart rate and cardiac time intervals: overall mean (SD) mean values, maximum and minimum values, and p values for respiratory groups 1–8*

		Respiratory group								
	Mean (SD)	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*p <*
HR	80 4 (9 75)	80 1	82 8*	82 0	82 2	80 8	79 3	78 9	77 2†	0 0001
RR	758 (90 5)	759	734†	742	742	754	768	770	793*	0 0001
PEP	81 2 (13 6)	80 3	83 1	84 1	85 0*	81 3	78 4†	79·0	78 5	0 0001
IVC$_c$	0 4 (11·4)	−0 4	2 9	4 6*	4·5	0 8	−2 3	−1·3	−5·3†	0 0001
LVET$_c$	−0·3 (10 1)	−0 7	−1 7	−3 9	−4 0†	1 1	4 0*	2 4	0 8	0 0001
IVR$_c$	0 4 (9 7)	2 4*	1 7	0 0	−1 0	−2 0†	0 5	0 2	1 0	0 05
LVFT$_c$	−0 1 (19 5)	−0 2	−3 5†	0 2	−0 2	−0 6	−2 0	−0 2	5·9*	0 01

*Maximum. †Minimum.
HR, heart rate, c, corrected See table 1 for abbreviations.

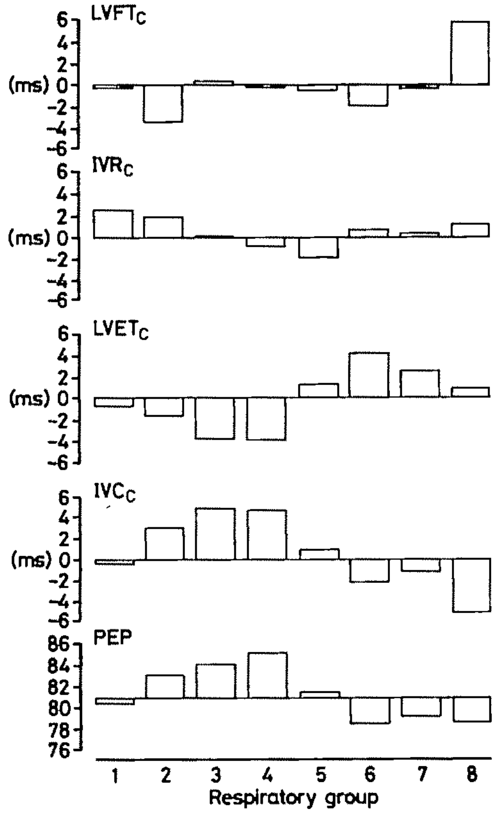

Fig 3 Values of the cardiac time intervals in respiratory groups 1–8. PEP, pre-ejection period; IVC_C, corrected isovolumic contraction time; $LVET_C$, corrected left ventricular ejection time; IVR_C, corrected isovolumic relaxation time; $LVFT_C$, corrected left ventricular filling time.

period (group 6), it reached a minimum at the transition from expiration to inspiration (group 8) at a point when the filling time was at its maximum (see below).

LEFT VENTRICULAR EJECTION TIME

The values for ejection time tended to be the reverse of those of isovolumic contraction and the pre-ejection period. Values were lowest at the end of inspiration (groups 3 and 4) and highest around mid-expiration (group 6). This reversal, in comparison with the other systolic time intervals does not apply to groups 7, 8, and 1: values for the ejection time became progressively less through the second half of expiration and this trend continued well into inspiration.

ISOVOLUMIC RELAXATION TIME

Isovolumic relaxation time did not vary as much as other invervals. It reached a maximum in the first half of inspiration (group 1) and a minimum in the first half of expiration (group 5).

LEFT VENTRICULAR FILLING TIME

The values for filling time showed little or no variation apart from the maximum value which occurred at the beginning of inspiration (group 8), and the minimum which occurred in the second half of inspiration (group 3).

Discussion

HEART RATE

In earlier studies of respiration and systolic time intervals, respiratory arrhythmia did not produce a significant change of heart rate between mid-inspiration, mid-expiration, and end-expirations.[13,14] We believe that the difference between these results and the ones that we obtained may be because we compared the values of eight different respiratory phases rather than just the values during inspiration and expiration. We found that the greatest difference in heart rates occurred between beats at the changeover between expiration and inspiration (group 8, 77·2 beats/min) and those in the second half of inspiration (group 2, 82·8 beats/min) (table 2). We found no significant difference between mid-inspiratory (groups 1 and 2, 81·0 beats/min) and mid-expiratory (groups 5 and 6, 80·1 beats/min) heart rates ($p < 0{\cdot}1$).

Posture may be another explanation for the differences between our study and earlier studies. Others have shown that several cardiac variables differ significantly depending on whether they are measured while the subject is supine or sitting.[15–17] It is therefore not unreasonable to expect that respiration will have a greater effect on heart rate in the sitting position than in the supine. The difference between maximum and minimum heart rates was 5·6 beats/min; this was considerably higher than the difference measured by others in supine subjects.[3,13]

SYSTOLIC TIME INTERVALS

Our results confirm previous studies that found a decrease in left ventricular ejection time and a simultaneous increase in the pre-ejection period during inspiration.[1–3] An understanding of the effect of inspiration on systolic function aids the interpretation of these results.[18] An increase of relative afterload owing to the decrease in pleural pressure would require a longer period of contraction to overcome this relative increase in aortic pressure. This delay in aortic valve opening is reflected in the increase of both the pre-ejection period and the isovolumic contraction time. For the same reason the aortic valve will close sooner, resulting in shorter ejection times. On the other hand, when pleural pressure conditions are reversed at the beginning of expiration, the values of the systolic time interval are reversed.

The behaviour of these intervals is symmetrical except for the second half of expiration. It is not obvious why ejection values become progressively smaller. Furthermore, in the second half of expiration pre-ejection period values remain relatively constant and isovolumic contraction produces a markedly lower value at the changeover between expiration and inspiration. As mid-expiration seems to be the turning point for these developments, we studied the beats in the second half of expiration more closely. We examined two consecutive beats when inspiration began during the isovolumic relaxation or filling time (that is in diastole) of the second beat. The systoles of both beats therefore lay in the second half of expiration. Table 3 shows that the systolic time intervals of these two beats were not significantly different. We assume, therefore, that the variation in the values of systolic time interval in the second half of expiration (groups 6 and 7) is more or less random. This could well be a result of the intrathoracic pressure conditions produced by end expiratory apnoea.

We also studied the pronounced drop in the isovolumic contraction time in group 8 by examining consecutive beats in which the inspiration started in systole (that is during either isovolumic contraction or ejection time). When inspiration started in the ejection time of the second beat, the duration of this interval decreased significantly ($p < 0.01$). Isovolumic contraction also shortened, although not significantly. The drop in both values (when a drop in one value would be expected to be accompanied by an increase in the other) can be explained by the fact that isovolumic contraction still occurs in expiration whereas ejection time is already affected by the inspiratory drop in pleural pressure. This means that the opening of the aortic valve occurs under expiratory pleural pressure conditions whereas there is premature closure of the aortic valve because of the increasing left ventricular aortic pressure gradient. This would explain why the value for isovolumic contraction time in group 8 is low; that it is the lowest may merely be the result of the end-expiratory fluctuation found in groups 6 and 7 (see above).

If all of systole occurs in inspiration—that is inspiration starts during isovolumic contraction and both intervals are affected by the decrease in pleural pressure—the difference in isovolumic contraction time between the two beats increases, whereas the difference in ejection time decreases. These differences were not statistically significant; but this was probably because there were too few subjects in whom inspiration started during isovolumic contraction for such a difference to become apparent (table 3).

Table 3 *Differences (ms) between the respective intervals of two consecutive end expiratory beats when inspiration started during the second beat*

	Inspiration started in:			
	IVC (n=5)	*LVET (n=23)*	*IVR (n=8)*	*LVFT (n=25)*
PEP	0·0	0·0	0·3	−0·8
IVC	1·0	−1·7	2·6	−0·7
LVET	−1·4	−2·7*	−0·6	0·0
IVR	4·6	−0·2	−0·9	1·1
LVFT	−4·0	6·9†	5·3	1·3

*p < 0·01, †p < 0·05
n, number of subjects in whom the start of inspiration occurred during this interval.
See table 1 for abbreviations.

DIASTOLIC TIME INTERVALS

The high levels of significance for the associations between systolic time intervals and phase of respiration reflect the fact that the contractile phase of the cardiac cycle is more dependent on respiration than the relaxation and filling phase. Analysis of variance showed that the isovolumic relaxation time, although dependent on respiration, is the least affected of all the cardiac time intervals. In normal subjects this interval was reported to be stable during and after exercise[19]; this was also true over a large range of RR intervals in patients with atrial fibrillation.[20 21] The isovolumic relaxation time, however, varies increasingly in patients with ischaemic heart disease,[22] left ventricular hypertrophy,[23 24] hypertrophic cardiomyopathy,[21 25 26] or aortic valve disease.[19] This shows that heart disease may affect respiratory modulation of isovolumic relaxation.

The peak isovolumic relaxation values did not occur in the respiratory groups in which the peak values of the other intervals were found. The maximum and minimum values occurred when other intervals were changing. The mechanisms of this phase shift are not clear.

Left ventricular filling time is strongly dependent on RR interval (that is heart rate).[19 20] After correction for RR interval the filling times reflect this strong dependency over most of the respiratory cycle. The higher values at the start of inspiration and the lower values in the second half of inspiration imply that respiration induces changes in filling of the left ventricle. Previous studies in which the end diastolic volume, area, or dimensions were measured by sonomicrometer measurements,[9 12] radionuclide methods,[27] mechanical transducers,[28] or echocardiography[29-31] during normal inspiration found either no change or a decrease in these diastolic variables. A shortened filling time in the second half of inspiration does not contradict these findings. However, the increase in filling at the start of inspiration is unexpected. But the earlier studies did not consider beats in which inspiration started. It was in these beats that filling time was significantly prolonged (table 3). In such beats the ejection time is immediately shortened by the increasing pressure gradient between left ventricular and aortic pressure. The next isovolumic relaxation remains effectively unchanged and the filling time is significantly prolonged. This may be explained by the efficient initial contraction of the left ventricle during the isovolumic contraction which still takes place in expiration—that is before the relative increase in afterload occurs. The lack of change in isovolumic relaxation is consistent with the model of a coupling between contraction and relaxation. This coupling has been described on the basis of the release and subsequent uptake of calcium by the sarcoplasmic reticulum.[32-34] More recently it has also been postulated that during contraction energy stored in the microstructure of the cardiac muscle cell and in the connective tissue surrounding the cells is released during diastole actively to relax and expand the heart.[35] This energy stored during the end expiratory isovolumic contraction would accordingly result in an unchanged isovolumic relaxation despite the fact that inspiration has already begun. It would also maintain the factors responsible for fast filling during end expiration and, together with the fact that the left atrium is still well filled,[36] lead to a filling time typical of end expiration. Apart from a shortened ejection time, such beats would therefore display the characteristics of an end expiratory beat. The decrease in ejection time implies a shorter RR interval and, as filling time is highly dependent on RR interval, the corrected filling time is in fact longer than it would normally be for a beat of this duration. If on the other hand a beat occurs completely after the start of inspiration, the intrathoracic pressure affects not just ejection but the complete left ventricular systole, with the consequences for relaxation and filling (table 3).

The measurement of the cardiac time intervals over the complete respiratory cycle leads to a better understanding of the respiratory modulation of the systolic time intervals. The results accord with the idea that a relative increase in afterload is the primary factor influencing left ventricular systolic function during inspiration. We also found changes in the diastolic time intervals that had not previously been reported, particularly in filling behaviour at the start of inspiration. This may be viewed as having a compensatory effect. At the transition from expiration to inspiration the RR interval shortens considerably. Because the filling time is highly dependent on RR interval, filling time would normally decrease more than the other intervals. When inspiration occurs in ejection time, however, only this interval shortens whereas the other intervals maintain their expiratory character. Therefore filling time is de facto longer than it would normally be for a beat of this length. An increase in filling at this point in the respiratory cycle would help to offset in part the loss of efficiency of left ventricular function during inspiration.

References

1 Weissler AM, Peeler RG, Roehl WH. Relationship between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease. *Am Heart J* 1961;**62**: 367–71.

2 Carter WH, McIntosh HD, Orgain ES. Respiratory variation of left ventricular ejection time in patients with pericardial effusion. *Am J Cardiol* 1972;**29**: 427–31.

3 Nandi PS, Pigott VM, Spodick DH. Sequential cardiac responses during the respiratory cycle: patterns of change in systolic intervals. *Chest* 1973;**63**:380–5.

4 Franklin DL, Van Citters RL, Rushmer RF. Balance between right and left ventricular output. *Circ Res* 1962;**10**:17–26.

5 Guntheroth WG, Morgan BC, Mullins GL. Effect of respiration on venous return and stroke volume in cardiac tamponade. *Circ Res* 1967;**20**:381–90.

6 Ruskin J, Bache RJ, Rembert JC, Greenfield JC. Pressure-flow studies in man: effect of respiration on left ventricular stroke volume. *Circulation* 1973;**48**: 79–85.

7 Shabetai R, Fowler NO, Fenton JC, Masangkay M. Pulsus paradoxus. *J Clin Invest* 1965;**44**:1882–98.

8 Santamore WP, Lynch PR, Meier G, Heckman J, Bove AA. Myocardial interaction between the ventricles. *J Appl Physiol* 1976;**4**:362–8.

9 Summer WR, Permutt S, Sagawa K, Shoukas AA, Bromberger-Barnea B. Effects of spontaneous respiration on canine left ventricular function. *Circ Res* 1979;**45**:719–28.

10 Robotham JL, Rabson J, Permutt S, Bromberger-Barnea B. Left ventricular hemodynamics during respiration. *J Appl Physiol* 1979;**47**:1295–303.

11 Karam M, Wise RA, Natajaran TK, Permutt S, Wag-

ner HN. Mechanisms of decreased left ventricular stroke volume during inspiration in man. *Circulation* 1984;**69**:866–73.

12 Olsen CO, Tyson GS, Maier GW, Davis JW, Rankin JS. Diminished stroke volume during inspiration: a reverse thoracic pump. *Circulation* 1985;**72**:668–79.

13 Pigott VM, Spodick DH. Effects of normal breathing and expiratory apnea on duration of the phases of the cardiac cycle. *Am Heart J* 1971;**82**:786–93.

14 Spodick DH, Paladino D, Flessas AP. Respiratory effects on systolic time intervals during pericardial effusion *Am J Cardiol* 1983;**51**:1033–5.

15 Upton MT, Rerych SK, Roeback JR, *et al*. Effect of brief and prolonged exercise on left ventricular function. *Am J Cardiol* 1980;**45**:1154–60.

16 Manyari DE, Kostuk WJ. Left and right ventricular function at rest and during bicycle exercise in the supine and sitting positions in normal subjects and patients with coronary artery disease. *Am J Cardiol* 1982;**51**:36–42.

17 Crawford MH, Petru MA, Rabinowitz C. Effect of isotonic exercise training on left ventricular volume during upright exercise. *Circulation* 1985;**72**: 1237–43.

18 Bromberger-Barnea B. Mechanical effects of inspiration on heart function: a review. *Fed Proc* 1981; **40**:2172–7.

19 Oldershaw PJ, Dawkins KD, Ward DE, Gibson DG. Diastolic mechanisms of impaired exercise tolerance in aortic valve disease. *Br Heart J* 1983;**49**:568–73.

20 Cieslinski A, Hui WKK, Oldershaw PJ, Gregoratos G, Gibson D. Interaction between systolic and diastolic time intervals in atrial fibrillation. *Br Heart J* 1984;**51**:431–7.

21 Alvares RF, Goodwin JF. Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta- adrenergic blocking drugs. *Br Heart J* 1982;**48**:204–12.

22 Mattheos M, Shapiro E, Oldershaw PJ, Sacchetti R, Gibson DG. Non-invasive assessment of changes in left ventricular relaxation by combined phono-, echo-, and mechanocardiography. *Br Heart J* 1982;**47**:253–60

23 Shapiro LM, McKenna WJ. Left ventricular hypertrophy. Relation of structure to diastolic function in hypertension. *Br Heart J* 1984;**51**.637–42.

24 Moore RB, Shapiro LM, Gibson DG. Relation between electrocardiographic repolarisation changes and mechanical events in left ventricular hypertrophy. *Br Heart J* 1984;**52**:516–23.

25 Hanrath P, Mathey DG, Kremer P, Sonntag F, Bleifeld W. Effect of verapamil on left ventricular isovolumic relaxation time and regional left ventricular filling in hypertrophic cardiomyopathy. *Am J Cardiol* 1980;**45**:1258–63.

26 Betocchi S, Bonow RO, Bacharach SL, Rosing DR, Maron BJ, Green MV. Isovolumic relaxation period in hypertrophic cardiomyopathy: assessment by radionuclide angiography *J Am Coll Cardiol* 1986;**7**:74–81.

27 Sharf SM, Brown R, Saunders N, Green LH Effects of normal and loaded spontaneous inspiration on cardiovascular function. *J Appl Physiol* 1979;**47**:582–90.

28 Wead WB, Norton JF. Effects of intrapleural pressure changes on canine left ventricular function. *J Appl Physiol* 1981;**50**:1027–35.

29 Brenner JI, Waugh RA. Effect of phasic respiration on left ventricular dimension and performance in a normal population. *Circulation* 1978;**57**:122–7.

30 Brinker JA, Weiss JL, Lappe DL, *et al*. Leftward septal displacement during right ventricular loading in man. *Circulation* 1980;**61**:626–33.

31 Jardin F, Farcot JC, Boisante L, Prost JF, Gueret P, Bourdarias JP. Mechanism of paradoxic pulse in bronchial asthma. *Circulation* 1982;**66**.887–94.

32 Parmley WW, Sonnenblick EH. Relation between mechanics of contraction and relaxation in mammalian cardiac muscle. *Am J Physiol* 1969;**216**: 1084–91.

33 Yellin EL, Sonnenblick EH, Frater RWM. Dynamic determinants of left ventricular filling: an overview. In: Baan J, Arntzenius AC, Yellin EL, eds. *Cardiac dynamics*. The Hague: Martinus Nijhoff, 1980: 145–58.

34 Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation. implications in cardiac disease. *Circulation* 1983;**69**:190–6

35 Robinson TF, Factor SM, Sonnenblick EH. The heart as a suction pump. *Scientific American* 1986;**254**: 62–9.

36 Ishida Y, Meisner JS, Tsujioka K, *et al*. Left ventricular filling dynamics: influence of left ventricular relaxation and left atrial pressure. *Circulation* 1986;74.187–96.

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Use of a double balloon technique for percutaneous balloon pulmonary valvotomy in adults

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SUMMARY Percutaneous double balloon pulmonary valvotomy was performed on seven consecutive adult patients (mean age 26 years) with congenital pulmonary valve stenosis. The peak systolic transvalvar pressure gradient was significantly reduced from a mean (SD) of 104 (30) to 24·3 (6) mm Hg. This haemodynamic improvement was maintained at six week follow up. In six patients pulmonary infundibular spasm developed immediately after valvotomy; however, these patients showed considerable haemodynamic improvement at the six week follow up. During balloon inflation the heart rate did not fall below 60 beats/minute and the systemic aortic pressure was maintained above 90 mm Hg.

Early results indicate that percutaneous double balloon valvotomy in adults is an effective treatment for isolated pulmonary valve stenosis. Theoretically the two balloons provide a venting area during inflation. This has the advantage of preventing bradycardia or systemic hypotension during prolonged balloon inflation.

Percutaneous balloon pulmonary valvotomy with a single balloon was first performed by Kan *et al* in a child[1] and by Pepine *et al* in an adult.[2] Percutaneous balloon valvotomy has been the treatment of choice for congenital pulmonary valve stenosis in 96 consecutive children in our centre.[3]

We have already reported the use of the double balloon valvotomy technique for mitral valve stenosis.[4] We now describe our experience in seven consecutive adult patients with congenital pulmonary valve stenosis in whom we used a double balloon technique for percutaneous pulmonary valvotomy.

Patients and methods

Seven consecutive adult patients (two women and five men; mean age 26 years, range 15–37) with congenital pulmonary valve stenosis (table 1) had transluminal double balloon pulmonary valvotomy. Their main complaints were palpitation and shortness of breath on exertion (class II New York Heart Association classification). All patients had a systolic thrill in the pulmonary area and a soft pulmonary second heart sound with a grade 4 to 5 or 6 ejection systolic murmur. In all patients the electrocardiogram showed right axis deviation with right ventricular hypertrophy. The cross sectional echocardiogram showed a domed pulmonary valve and right ventricular hypertrophy.

TECHNIQUE OF VALVOTOMY

Signed consent was obtained on a special procedure consent form. All the patients were given 10 mg oral diazepam as premedication, and the procedures were performed under local anaesthesia. A 7F sheath was introduced percutaneously through the right femoral vein. Two 7F sheaths were similarly introduced through the left femoral vein. A 7F pigtail catheter was introduced percutaneously via the right femoral artery into the aorta for continuous pressure monitoring. Heparin (5000 units) was given intraarterially.

A 7F Berman angiography catheter was advanced from the left femoral vein and positioned in the right ventricle to monitor the right ventricular pressure during the procedure and for right ventricular angio-

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Table 1 *Clinical characteristics and pulmonary valve and balloon diameters in seven consecutive patients with congenital pulmonary valve stenosis*

Patient No	*Age*	*Sex*	*Pulmonary valve diameter (mm)*	*Two balloon diameter (mm)*
1	32	M	27	15 + 15
2	15	F	24	12 + 15
3	35	M	27	15 + 15
4	28	F	18	12 + 12
5	18	M	19	(a) 10 + 10* (b) 10 + 15
6	37	M	28	(a) 15 + 15* (b) 15 + 18
7	20	M	27	15 + 15

*Two balloon combinations used; a, first combination; b, second combination.

graphy in the anteroposterior and lateral projections before and after valvotomy. Pulmonary artery, right ventricular, and aortic pressures were recorded simultaneously, followed by pull-back pressures from the pulmonary artery to right ventricle before and after dilatation and six weeks after the procedure.

We selected a balloon size that was appropriate to the diameter of the pulmonary valve annulus, which was estimated by cross sectional echocardiography and a biplane cinevideo angiogram. A grid was recorded on the angiogram so that the pulmonary valve annulus could be correctly measured. For all the patients the sum of the diameters of the balloon catheters used for successful valvotomy was 3–5 mm more than the diameter of the pulmonary valve annulus. The first combination of balloons used on patients 5 and 6 failed to produce adequate dilatation (table 1). Two 7F Berman wedge pressure catheters were advanced from the right and left femoral veins and positioned in the left pulmonary artery. Through each catheter a 0·038 inch diameter preshaped Teflon coated exchange guide wire was introduced and positioned well into the pulmonary artery in the left lower lobe. The catheters and the introducer sheaths were then removed, leaving the guide wires in position in the left pulmonary artery.

We used two 9F Meditech balloon catheters (10–18 mm diameter) (table 1) attached through a pressure gauge to a 20 ml syringe filled with diluted (20%) contrast material. The balloon catheters were then advanced over the guide wires across the stenotic pulmonary valve. The guide wires remained in the left pulmonary artery.

The two balloons were positioned across the pulmonary valve by biplane fluoroscopy. Then they were simultaneously inflated to 4–6 atmospheres for 8–10 seconds (mean 5 dilatations) (fig 1). During inflation the right ventricular and aortic pressures were continuously monitored. After dilatation the balloon catheters were withdrawn over the exchange wires and replaced by two 7F sheaths.

CROSS SECTIONAL ECHOCARDIOGRAPHY

Before valvotomy, on the day after valvotomy, and 6–8 weeks later we obtained cross sectional echocardiograms using a Hewlett Packard phased array system with 3·5–5 MHz transducers. Standard views were obtained; the short axis left parasternal view was used to estimate the diameter of the pulmonary valve annulus and the excursion of the leaflets. The images were recorded for subsequent analysis. ATL pulsed Doppler was used to detect pulmonary regurgitation before valvotomy, immediately after valvotomy, and at a six week follow up.

We used paired *t* tests for statistical analysis.

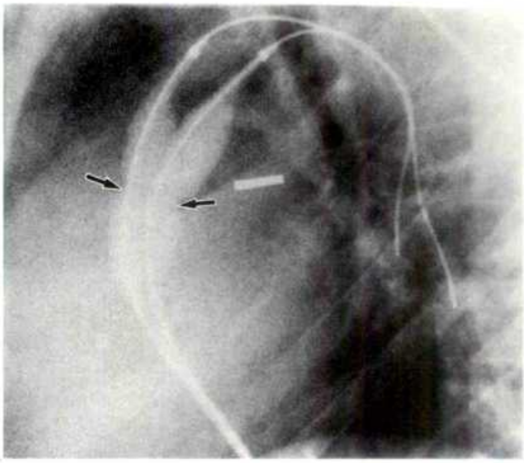

Fig 1 *Lateral projection of the heart with inflated balloons positioned across the pulmonary valve; note the indentation (arrowed) of the balloon produced by the stenotic valve.*

Results

CLINICAL

At clinical evaluation immediately after pulmonary valvotomy the systolic thrill in the pulmonary area had disappeared in all but two patients (cases 2 and 7). In these patients the thrill had disappeared at the six week follow up. There was a snapping pulmonary second heart sound in all patients and no patient developed an early diastolic murmur after valvotomy. Furthermore, the duration and intensity of the systolic murmur decreased in all patients.

HAEMODYNAMIC, ANGIOGRAPHIC, AND ECHOCARDIOGRAPHIC RESULTS

After balloon valvotomy all seven patients had haemodynamic evidence of relief of the pulmonary valve stenosis. The peak systolic gradient across the pulmonary valve decreased from a mean of 104 (30) to 24·3 (6) mm Hg ($p < 0.001$). The improvement was maintained at the six week follow up study (fig 2). Right ventricular systolic pressure decreased from a mean of 120 (28) to 69 (25) mm Hg ($p < 0.009$) (table 2; fig 3).

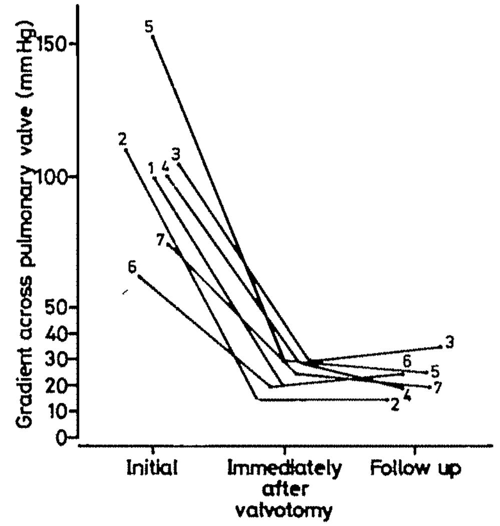

Fig 2 *Decrease in peak systolic pulmonary gradient immediately after double balloon valvotomy and at six weeks' follow up.*

Echocardiography and a right ventricular angiogram demonstrated that although the pulmonary valve still appeared to be thickened in all patients, there was good excursion of the valve leaflets (fig 4), indicating successful dilatation. Pulsed Doppler revealed mild pulmonary regurgitation in patients 1 and 4 after dilatation.

Pull back pressure measurements from the pulmonary artery to the right ventricular outflow and then to the right ventricular apex showed the presence of infundibular spasm in patients 2–7 immediately after successful pulmonary valvotomy; the gradient was small in patients 3–7. Haemodynamic follow up studies of patients 2–7 at six weeks showed that there was a further reduction in the right ventricular systolic pressures from the immediate post-valvotomy mean of 69 (25) to 47 (11) mm Hg, which was suggestive of relief of the infundibular spasm (table 2). This contrasts with the gradients across the pulmonary valve, where the major reduction occurred immediately after valvotomy (fig 2; fig 5). In patient 2 the infundibular spasm was severe, but was completely relieved during six weeks treatment with oral propranolol 20 mg three times a day.

During double balloon inflation, no patient had bradycardia (heart rates >60 beats/min) and aortic systolic pressure was maintained above 90 mm Hg (fig 6).

Table 2 *Haemodynamic data before (B), immediately after balloon pulmonary valvotomy (A), and at six weeks' follow up (F)*

	RVSP			*PSPG*			*HR*		
Patient No	*B*	*A*	*F*	*B*	*A*	*F*	*B*	*A*	*F*
1	120	40	—	100	20	—	86	90	—
2	130	120*	30	110	15	15	92	98	64
3	125	75*	65	105	30	35	96	80	74
4	120	65*	50	100	30	20	98	84	70
5	170	60*	47	153	30	27	105	105	86
6	80	60*	45	62	20	25	75	64	54
7	95	62*	43	75	25	20	80	88	62
Mean (SD)	120 (28)	69 (25)	47 (11)	104 (30)	24 3 (6)	23 6 (7)	90 (11)	87 (13)	68 (11)
p value	B *vs* A, <0·009; B *vs* F, <0 003;			B *vs* A, <0 001, B *vs* F, < 0 003,			B *vs* A, NS, B *vs* F, <0 001.		

*Infundibular spasm.
RVSP, right ventricular (apical) systolic pressure, PSPG, peak systolic pulmonary valvar gradient; HR, heart rate.

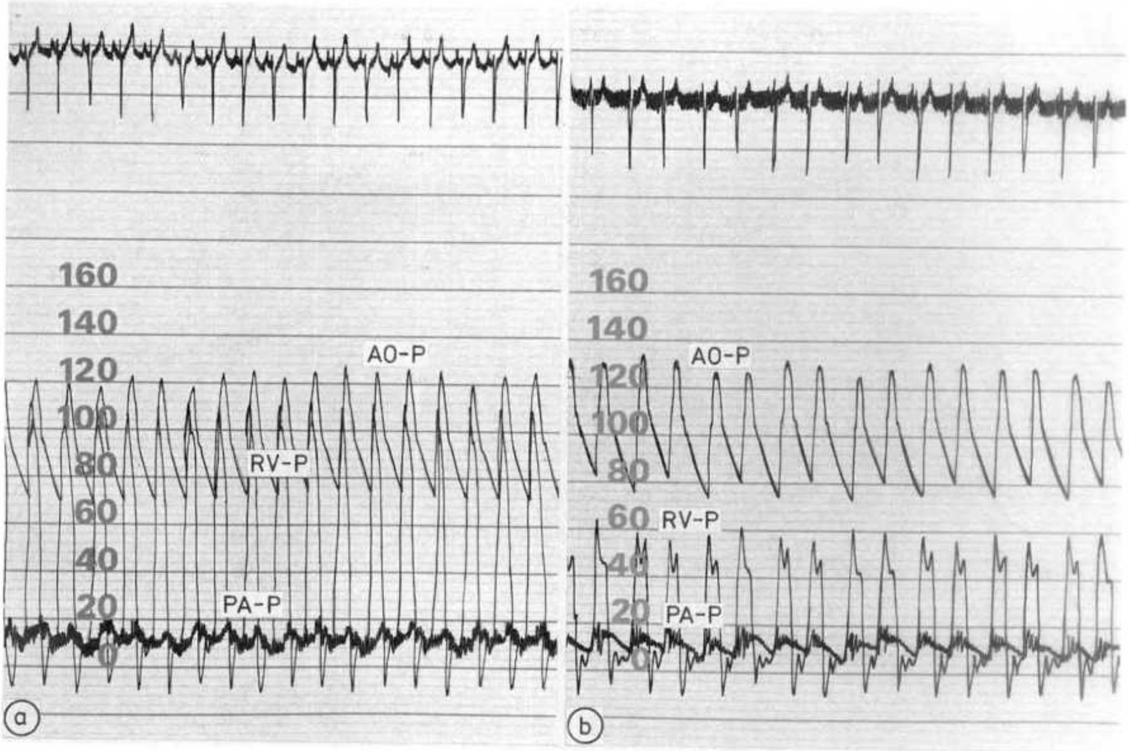

Fig 3 *Aortic (AO-P), right ventricle (RV-P), and pulmonary artery (PA-P) pressure tracing (a) before and (b) after pulmonary valvotomy. There was a considerable reduction of right ventricular pressure and gradient across the pulmonary valve (patient 3).*

Discussion

When Tynan *et al* used a single balloon for pulmonary valvotomy, hypotension developed in 26 of 27 patients during inflation of the balloon and severe bradycardia developed in 12 patients.[5] This complication was confirmed in another recent study.[6] When we used a double balloon technique neither bradycardia nor systemic hypotension developed in any of our patients. In all seven patients there was a dramatic improvement in the gradient across the pulmonary valve with no clinical evidence of pulmonary regurgitation.

The sum of the cross sectional area of two 10 mm balloon catheters (157 mm^2) is 50% less than that of a single 20 mm balloon catheter (314 mm^2) (fig 7). The double balloon technique thus theoretically provides a venting area between the balloons during inflation and thus ensures that the pulmonary valve orifice is not completely occluded, as it is by a single balloon. We presume that this is the mechanism by which bradycardia and hypotension are prevented during inflation. The procedure was successful when we used two balloons with a combined cross sectional area less than that of the single balloon which theoretically would otherwise have been required. It appears that the combined diameter of the two balloons, rather than their cross sectional area, is the determining factor for the success of valvotomy.

Ring *et al* demonstrated that overdilatation of the pulmonary valve annulus in lambs by single oversized balloons, with a diameter that exceeded that of the annulus by 20–40%, damaged the heart.[7] In man Ben-Shachar *et al* demonstrated that balloons with diameters that were 20% larger than the diameter of the pulmonary valve annulus produced adequate dilatation with minimal damage to the subvalvar region.[8] The use of a double balloon technique which allows the use of two balloons with smaller total cross sectional areas than a single balloon (fig 7) must improve the safety of the procedure.

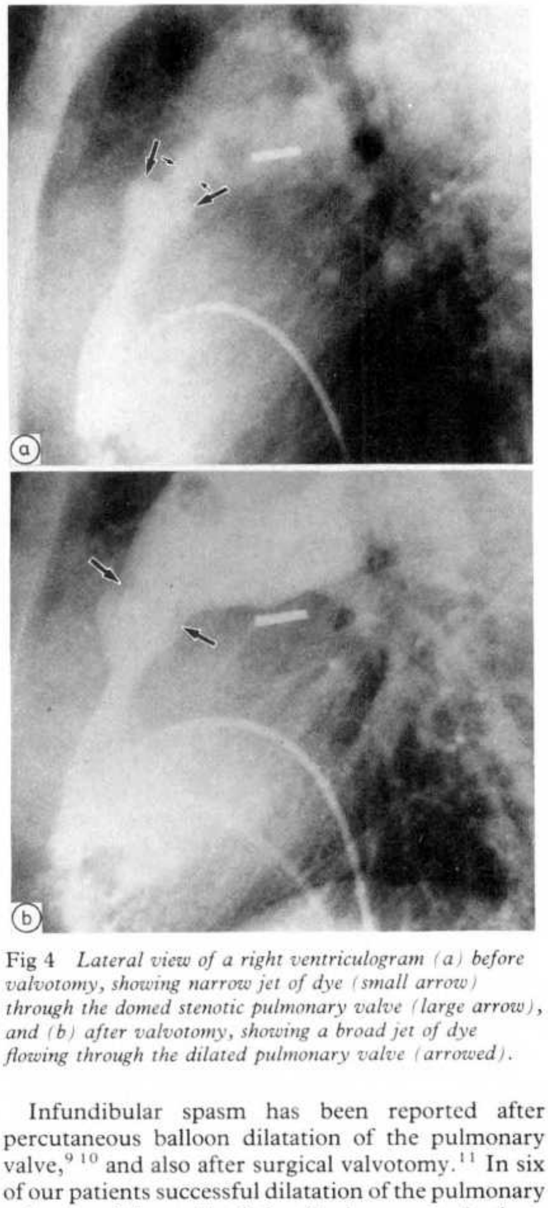

Fig 4 *Lateral view of a right ventriculogram (a) before valvotomy, showing narrow jet of dye (small arrow) through the domed stenotic pulmonary valve (large arrow), and (b) after valvotomy, showing a broad jet of dye flowing through the dilated pulmonary valve (arrowed).*

Infundibular spasm has been reported after percutaneous balloon dilatation of the pulmonary valve,[9 10] and also after surgical valvotomy.[11] In six of our patients successful dilatation of the pulmonary valve was followed by infundibular spasm. In these patients the right ventricular pressure resembled the systemic pressure, as in the case reported by Ben-Shachar *et al.*[8] Because β blockade in patient 2 relieved severe infundibular spasm after valvotomy it is conceivable that the use of prophylactic β blockade before valvotomy may prevent infundibular spasm. This requires further investigation.

In most adults the pulmonary valve annulus is bigger than the maximum available size of single balloon that is needed for successful dilatation, and two balloons will be necessary. We have shown that

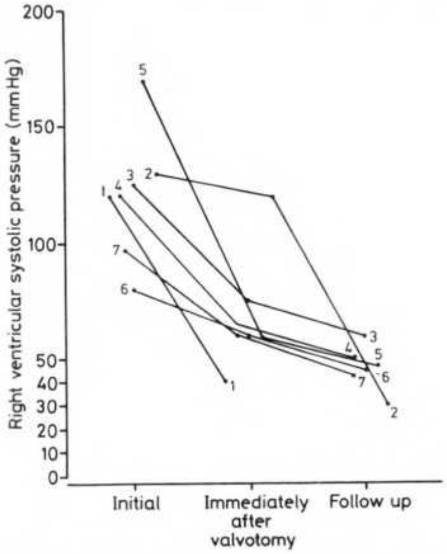

Fig 5 *Significant reduction in right ventricular (apical) systolic pressure immediately after double balloon valvotomy and further significant reduction at six weeks' follow up.*

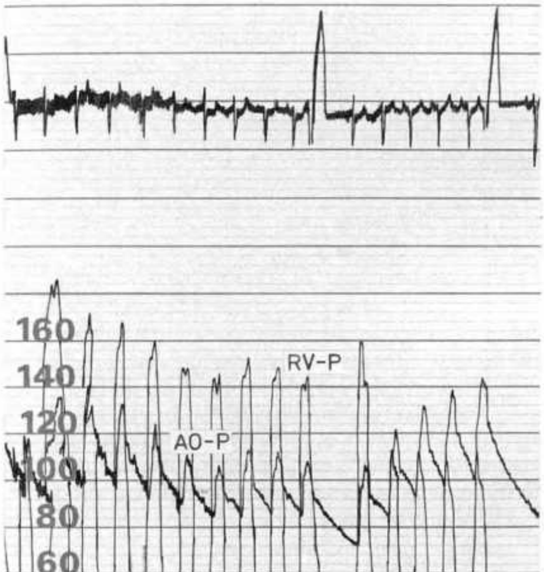

Fig 6 *Aortic (AO-P) and right ventricular (RV-P) pressure recordings during inflation of balloons. There was an insignificant drop in aortic pressure and heart rate remained normal.*

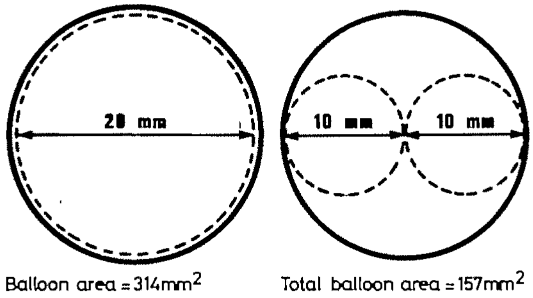

Fig 7 *Diagram comparing the cross sectional area of a 20-mm diameter balloon with that of two 10 mm balloons.*

percutaneous double balloon pulmonary valvotomy in adults is a safe and effective treatment for isolated pulmonary valve stenosis. All the demonstrable advantages of the double balloon technique indicate that this should become the choice for this procedure in adults.

Addendum

Since the submission of this paper we have performed another five successful percutaneous double balloon pulmonary valvotomies with similar results to those reported in this paper.

We thank Dr W Sawyer, for helping us to prepare the paper, and the cardiac catheter and echocardiography staff.

References

1 Kan JS, White RI, Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary-valve stenosis. *N Engl J Med* 1982;**370**:540–2.
2 Pepine CJ, Gessner I, Feldman RL. Percutaneous balloon valvoplasty for pulmonic valve stenosis in adults. *Am J Cardiol* 1982;**50**:1442–5.
3 Al Yousef S, Khan MA, Lababidi Z, Mullins CE, Mohareb J, Spencer J. Perkutane transluminale Ballondilatation der valvaeren Pulmonalstenose im Neugeborenen' und Kindersalter 2 jaerige Efahrung mit 96 Patienten [Abstract]. Jahres Tagung der Deutschen Gesellschaft fuer Kinderkardiologie, Aachen, September 1986, Hertz Kreislauf 1987;**19**:122.
4 Al Zaibag M, Ribeiro PA, Al Kasab S, Al Fagih MR. Percutaneous double-balloon mitral valvotomy for rheumatic mitral-valve stenosis. *Lancet* 1986; **i**.757–61.
5 Tynan M, Jones O, Joseph MC. Relief of pulmonary-valve stenosis in the first week of life by percutaneous balloon valvuloplasty. *Lancet* 1984;**i**.273.
6 Tynan M, Baker EJ, Rohmer J, *et al.* Percutaneous balloon pulmonary valvuloplasty. *Br Heart J* 1985;**53**:520–4.
7 Ring JC, Kulik TJ, Burke BA, Lock JE. Overdilatation of the pulmonary valve annulus with angioplasty balloons in the normal lamb [Abstract]. *Circulation* 1983;**68**(suppl III):III–394.
8 Ben-Shachar G, Cohen MH, Sivakoff MC, *et al.* Development of infundibular obstruction after percutaneous pulmonary balloon valvoplasty. *J Am Coll Cardiol* 1985;**3**:754–6.
9 Lababidi Z, Wu J. Percutaneous balloon pulmonary valvuloplasty. *Am J Cardiol* 1983;**52**:560–2.
10 Rocchini AP, Kveselis DA, Crowley D, *et al.* Percutaneous balloon valvuloplasty for treatment of congenital pulmonary valvar stenosis in children. *J Am Coll Cardiol* 1984;**3**:1005–12.
11 Campbell M, Brock R. The results of valvotomy for simple pulmonary stenosis *Br Heart J* 1955; **17**.229–46.

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Percutaneous mitral valvotomy in rheumatic mitral stenosis: a new approach

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SUMMARY Three patients with rheumatic mitral stenosis were treated with percutaneous mitral valvotomy. A Brockenbrough catheter was advanced transseptally into the left atrium and then into the left ventricle over a long guide wire. An angle wire loop retriever was advanced through a 10 Fr straight catheter via the femoral artery into the left ventricle. The retriever was used to catch the flexible end of the long guide wire. This end of the long guide wire was then drawn out of the right femoral artery by the retriever through the straight catheter. The straight catheter was left in the descending aorta; the Brockenbrough catheter was removed and a 7 Fr balloon catheter was introduced percutaneously over the long guide wire through the femoral vein. This balloon catheter was used for interatrial septal dilatation and right femoral venous dilatation. In two patients this catheter was replaced over the long guide wire with a 9 Fr Schneider-Medintag Grüntzig catheter (3 × 12 mm diameter when inflated) and in the other by a Mansfield (18 mm diameter when inflated). The procedure was well tolerated in these three patients and there were no complications. Haemodynamic function improved, there was appeciable decrease in dyspnoea, and exercise tolerance was increased.

This procedure has several advantages: the balloon is more easily positioned through the mitral valve; the stability of the balloon during inflation is improved by traction at both ends of the long guide wire; and there is the option of rapidly exchanging one balloon for a larger one over the long guide wire. This technique seems to be less arrhythmogenic and results in less blood loss because manual compression of the femoral vessels after the procedure is easier.

Closed or open mitral valvotomy are commonly used to treat mitral valve stenosis and the long term results are good.[1-3] Recently several workers have proposed percutaneous balloon dilatation as a treatment of valve stenoses, such as congenital pulmonary stenosis and congenital aortic stenosis, in children.[4-6] The results of balloon dilatation of the mitral valve are also good in adults and young patients with rheumatic valve stenosis.[7-12] Various techniques have already been used to achieve valvotomy. We describe a new technique for percutaneous balloon mitral valvotomy that we used in three cases of rheumatic mitral valve stenosis.

Patients and methods

CASE 1

A 44 year old white man with chronic rheumatic mitral valve disease was admitted to our hospital with increasing dyspnoea despite treatment with diuretics and vasodilators. He had a murmur indicating mitral stenosis without regurgitation. The electrocardiogram showed a sinus rhythm with left atrial hypertrophy. Echocardiographic studies revealed severe mitral stenosis with moderate thickening of the mitral leaflets and subvalvar apparatus. There was evidence of moderate enlargement of the diameter of the atrium (5 cm) but ventricular size and function were normal. Cardiac catheterisation was performed to evaluate the severity of the mitral stenosis. The mean gradient across the mitral valve during diastole (calculated by planimetry) was 23 mm Hg; cardiac output (calculated by thermodilution) was 4·8 l/min, and the calculated area of the mitral valve was 1·13 cm^2. Left ventriculography showed well preserved ventricular function and no evidence of mitral regurgitation. The results of coronary angiography were normal. A pulmonary arteriogram with venous phase showed moderate enlargement of the left atrium and no evidence of

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atrial mural thrombus. Surgical mitral valve commissurotomy was recommended but the patient refused. Treatment by percutaneous dilatation was then suggested. The patient agreed to the procedure and gave his informed consent.

CASE 2

A 62 year old woman who had had rheumatic valve disease since 1938 was admitted to our hospital for evaluation of mitral valve stenosis. For 24 months exertional dyspnoea had become progressively worse despite treatment with diuretics and vasodilators. There was a loud first heart sound with an opening mitral snap and a faint diastolic rumble of mitral stenosis. There was no evidence of pulmonary arterial hypertension. The electrocardiogram showed atrial fibrillation. Echocardiographic studies showed moderate mitral stenosis but the leaflets and subvalvar apparatus were not thickened. The diameter of the left atrium was enlarged (5·4 cm) but there was no evidence of mitral thrombus. Cardiac catheterisation showed a diastolic mean gradient across the mitral valve of 5 mm Hg, a cardiac output (calculated by thermodilution) of 1·7 l/min, and a calculated mitral valve area of 0·60 cm^2. An isoprenaline test was carried out. When the heart rate was 170 beats/min, the diastolic mean gradient across the mitral valve was 36 mm Hg and the calculated mitral valve area was 0·31 cm^2. Left ventriculography showed good ventricular function without evidence of mitral regurgitation. Coronary angiography was normal. The pulmonary arteriogram with venous phase showed a considerably enlarged left atrium and no evidence of atrial mural thrombus. After the procedure was discussed and explained the patient gave informed consent to percutaneous balloon dilatation of the mitral valve.

CASE 3

A 60 year old woman was admitted to our hospital with severe exertional dyspnoea and paroxysmal atrial fibrillation. There was a loud first heart sound followed by a grade 2/6 pansystolic murmur indicating mitral regurgitation. The pulmonary component of the second heart sound was increased and there was an opening snap and a diastolic rumble indicating mitral stenosis. The electrocardiogram showed sinus node rhythm with occasional premature supraventricular complexes, incomplete right bundle branch block, and hypertrophy of both atria. Cardiac fluoroscopy showed calcifications of the mitral valve. Cross sectional echocardiography showed severe mitral stenosis and calcification of the two leaflets and mitral annulus. There was no evidence of enlargement of the diameter of the left atrium (4·2 cm). Left ventricular function was well preserved and the right atrium and right ventricle were enlarged. The patient was treated with frusemide, a vasodilator, amiodarone, and an anticoagulant. Cardiac catheterisation showed pulmonary hypertension (systolic pulmonary pressure 115, diastolic 37, mean 62 mm Hg). The mean diastolic gradient across the mitral valve was 27 mm Hg, the cardiac output (thermodilution technique) was 3·4 l/min, and the calculated mitral valve area was 0·54 cm^2. Left ventriculography showed normal left ventricular function with moderate mitral valve regurgitation. Coronary angiography was normal. After the procedure was discussed and explained the patient gave informed consent to percutaneous balloon dilatation of the mitral valve.

Balloon dilatation procedure

Patients were premedicated with 30 mg of oral diazepam 30 minutes before the procedure. A 8 Fr pigtail catheter was advanced from the left femoral artery into the ascending aorta. The right heart was catheterised from the left femoral vein with a triple lumen Swan-Ganz catheter. Right heart oximetry series were performed. A 10 Fr straight catheter (Cook) was advanced into the left ventricle from the right femoral artery. A 8 Fr Brockenbrough catheter (USCI) was inserted into the left atrium through the right femoral vein by the transseptal catheter technique. Heparin (10 000 UI) was given. The Brockenbrough catheter was advanced into the left ventricle over a long guide wire (AHS: 400 cm long, 0·035 inch diameter). Then an angle wire loop retriever (Cook: 100 cm long, with a loop 25 mm diameter formed by 0·015 inch braided cable) was advanced through the 10 Fr straight catheter. The retriever was placed in the left ventricle and was used to catch the flexible end of the long guide wire. The retrieved end of the long guide wire was drawn out of the right femoral artery through the straight catheter. The straight catheter was left in the descending aorta (fig 1). Then the Brockenbrough catheter was removed and a 7 Fr balloon catheter (USCI: 7 mm diameter when inflated) was introduced percutaneously over the long guide wire by the venous approach. This balloon catheter allowed interatrial septal dilatation and dilated the right femoral vein at the puncture site. This catheter was replaced over the long guide wire by a 9 Fr Schneider-Medintag Grüntzig catheter (Sch-30226, Trefoil Meier, 100 cm long, 3 × 12 mm diameter when inflated). Another type of balloon catheter (Mansfield: 18 mm diameter when inflated) was used in the third patient. This balloon was inserted through the mitral valve over the long guide wire without difficulty. The balloon catheter was inflated to a pressure of 400

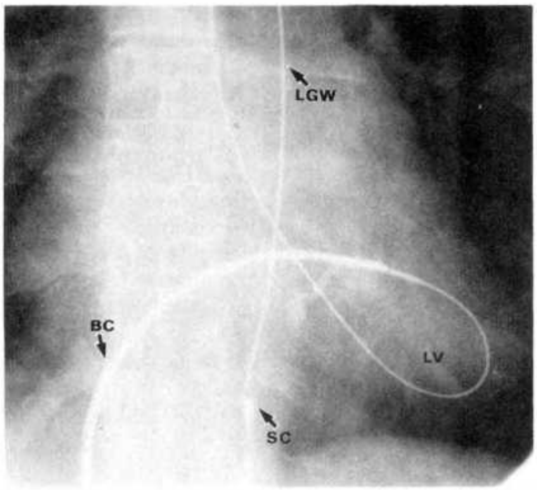

Fig 1 *Cineangiogram showing a long guide wire (LGW) pushed through the Brockenbrough catheter (BC) into the left ventricle (LV). The wire loop retriever was used to catch the flexible end of the long guide wire. The wire loop retriever and long guide were placed in the straight catheter (SC) positioned in the descending aorta.*

kPa with a 50% mixture of saline solution and contrast medium after the appropriate siting of the balloon was confirmed by a mid-balloon waist (fig 2). The balloon catheter was maintained in a good position by double traction applied to both ends of the long guide wire. The inflation-deflation cycle lasted 30 seconds to one minute. Five inflation-deflation cycles were applied at intervals of 2–3 minutes.

During each cycle the aortic and pulmonary capillary wedge pressures were continuously recorded. All three patients tolerated the procedure well. At the end of the procedure the balloon dilatation catheter was withdrawn over the wire and replaced by the Brockenbrough catheter left in the left atrium. The pigtail catheter introduced by the left femoral artery was advanced into the left ventricle. The mean mitral valve gradient was measured 20 minutes after the procedure. In case 2 the gradient was measured both at rest and after infusion of isoproterenol. Cardiac output was also measured by thermodilution. A new series of right heart oximetry measurements were obtained to find evidence of an atrial shunt from left to right. Left ventriculography was performed to assess mitral regurgitation. The arterial and venous catheters were removed. Haemostasis was achieved by direct compression and the patients were monitored in the intensive care unit for 24 hours.

Results

Percutaneous balloon dilatation of the mitral valve was well tolerated by our three patients and there were no complications. All three showed an appreciable decrease in dyspnoea and increased exercise tolerance. They were rapidly discharged. The clinical improvement was confirmed two months later. Case 1 needed no treatment and case 2 had only anticoagulant treatment. The table summarises the haemodynamic data before and after balloon dilatation of the mitral valve. Dilatation reduced the mean gradient across the mitral valve and increased the calculated mitral valve area in all three patients (at rest in cases 1 and 3 and after an isoproterenol test in case 2). Right heart oximetry showed a slight left to right atrial shunt in patients 1 and 2. Figures 3–5 show left ventricular and pulmonary capillary or left atrium pressures before and after balloon dilatation.

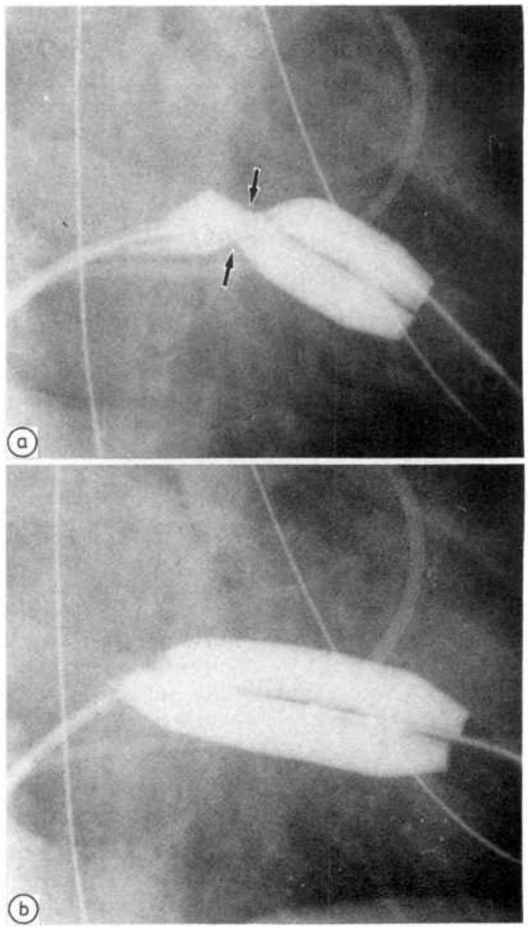

Fig 2 *Cineangiogram showing a trefoil balloon (3 × 12 mm in diameter) centred across the mitral valve. (a) The balloon was indented by the stenotic mitral valve (arrows). (b) Full inflation of the balloon.*

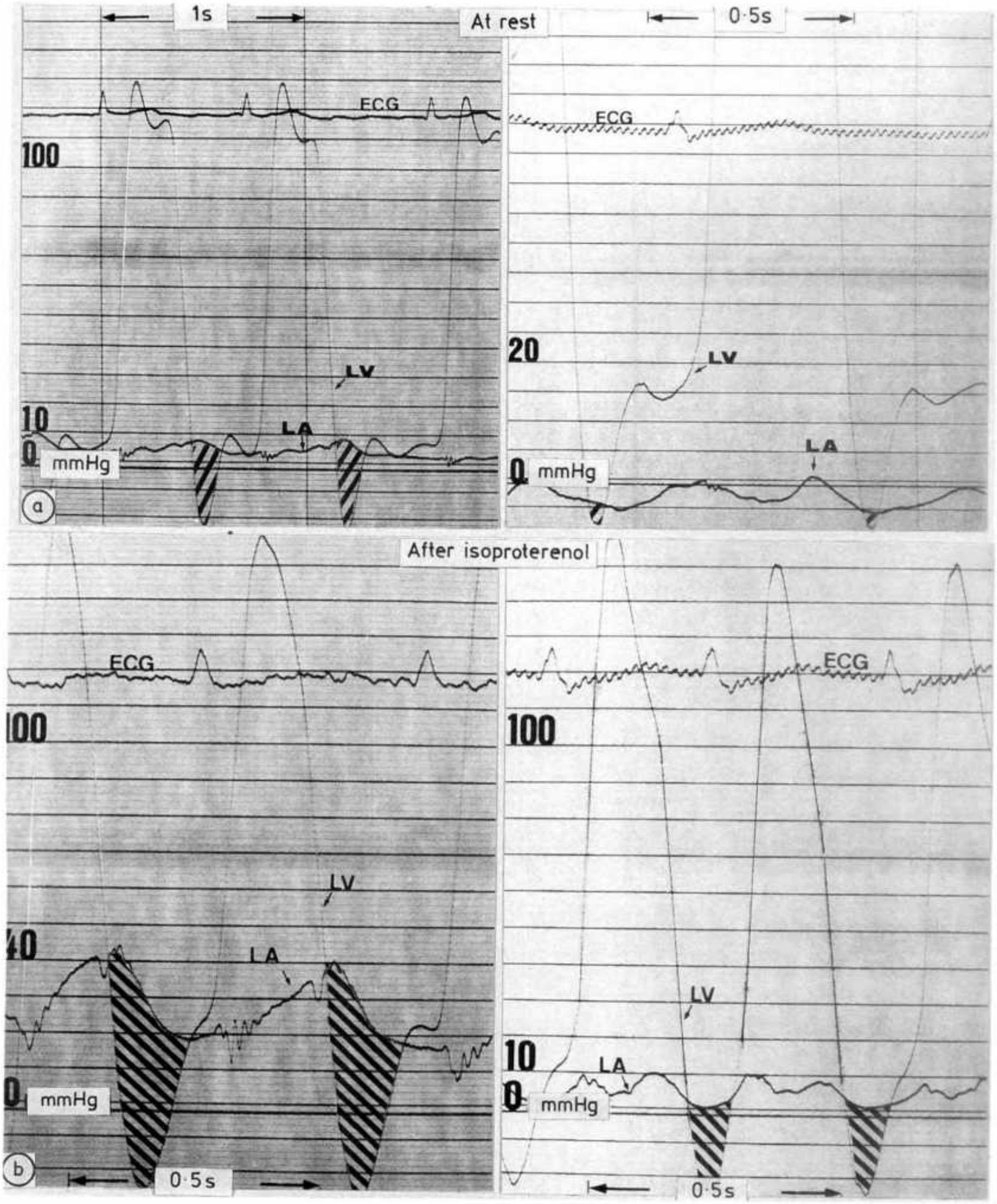

Fig 3 *Simultaneous left atrial (LA) and left ventricular (LV) pressures in case 1 before balloon dilatation of the mitral valve (a) and after balloon dilatation of the mitral valve (b) at rest and after isoproterenol.*

Discussion

The usual treatment for mitral stenosis is surgical intervention and surgical mitral commissurotomy remains a reliable treatment for pure mitral stenosis.[1-3] Recently in vitro and in vivo studies have shown the efficacy of mitral transvalvar dilatation by balloon catheter.[7 10 13] The percutaneous technique

Table *Haemodynamic data measured before and after valvotomy*

		Before valvotomy					*After valvotomy*			
Case No	*Age (y) and sex*	*Cardiac rhythm*	*HR*	*Mean LAP*	*MVA*	*MVG*	*HR*	*Mean LAP*	*MVA*	*MVG*
1	44 M	SR	77	25	1·13	23	97	18	1·80	10
2	62 F	AF	73	11	0·60	5	90	4	1·90	2
			157	24	0·31	36	176	4	1·07	15
3	60 F	SR	83	37	0·54	27	82	17	0·82	16

AF, atrial fibrillation; HR, heart rate (beats/min); LAP, left atrial pressure (mm Hg). MVA, mitral valve area (cm^2); MVG, mitral valve gradient (mm Hg); SR, sinus rhythm.

seems to be analogous to transvalvar dilatation by blunt dilatating instruments used during closed mitral commissurotomy. Various procedures have been used for percutaneous balloon dilatation of the mitral valve. The most usual technique is Inoue's procedure[7 8 11 12]: the balloon catheter is introduced through the femoral vein and positioned across the mital valve after passing through the atrial septum. This commonly causes a small interatrial shunt but there were no deleterious side effects in reported cases. It is often difficult to maintain the balloon catheter in the mitral annulus during balloon inflation.

Recently Babic *et al* have described a new technique for balloon dilatation in mitral stenosis.[10] The balloon catheter is inserted percutaneously from the left femoral artery over a long guide wire introduced into the right femoral vein, advanced transseptally to the left ventricle, and drawn out of the left ventricle, the aorta, and the femoral artery using a retriever set. According to Babic *et al* this procedure has several advantages: easy positioning of the balloon through the mitral valve, improved stability of the balloon during inflation by traction on both ends of the long guide wire, and no danger of creating an iatrogenic atrial septal defect. Nevertheless, Babic's technique

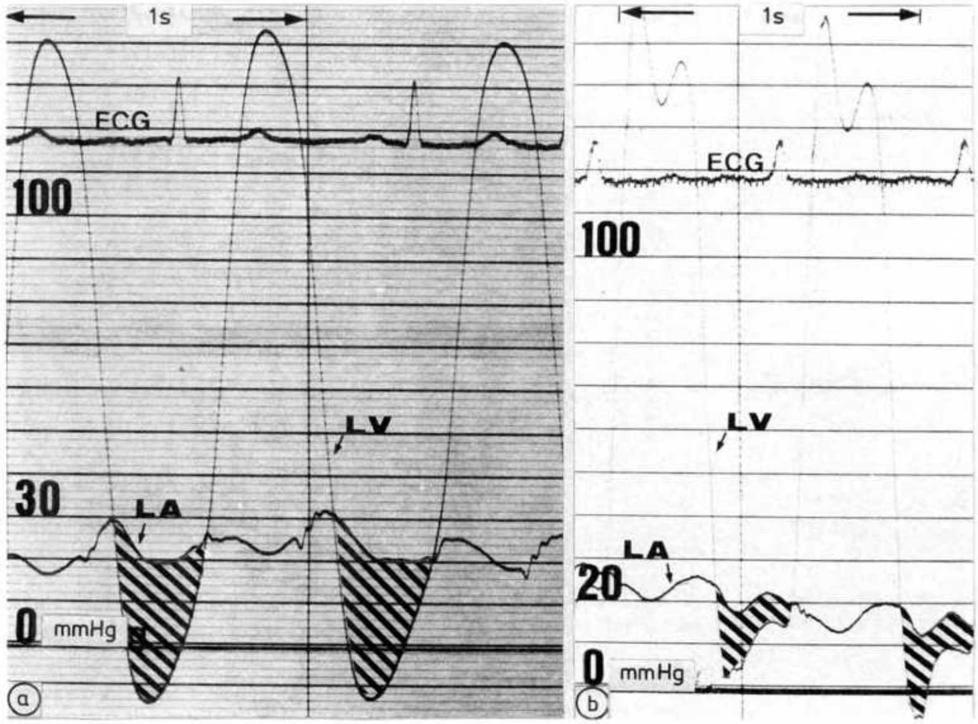

Fig 4 *Simultaneous left atrial (LA) and left ventricular (LV) pressures in case 2 before balloon dilatation of the mitral valve (a) and after balloon dilatation of the mitral valve (b).*

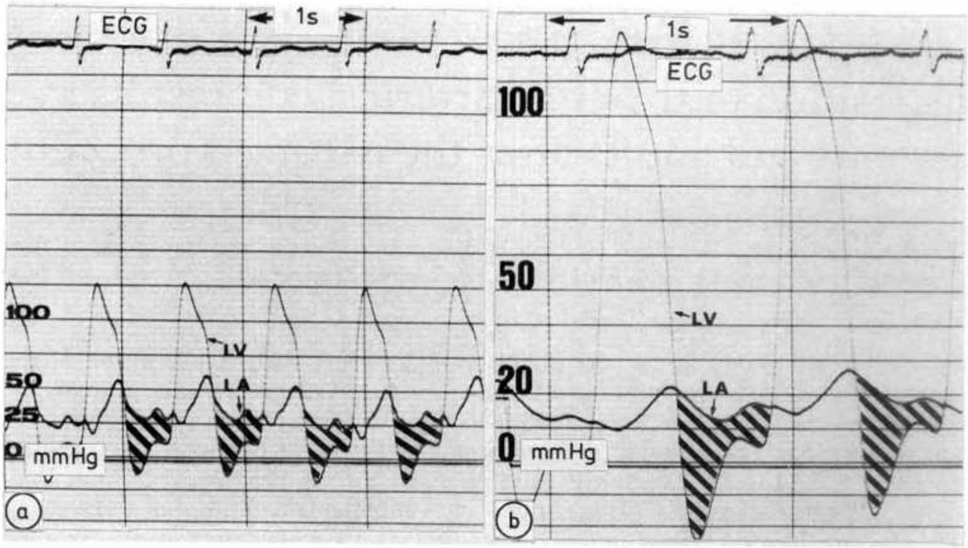

Fig 5 *Simultaneous left atrial (LA) and left ventricular (LV) pressures in case 3 before balloon dilatation of the mitral valve (a) and after balloon dilatation of the mitral valve (b).*

needs a femoral arterial approach with frequent local damage and considerable blood loss owing to the size of the balloon catheter. Our technique was inspired by Babic's technique but we use a femoral venous approach with transseptal technique for balloon introduction. With our technique there is also easier positioning, excellent stability of the balloon across the valve, and the option of rapidly exchanging an undersized balloon for a larger one over the long guide wire. Moreover, this technique seems to be less arrhythmogenic and, because it facilitates manual compression of the femoral vessels after the procedure, it reduces loss of blood. In our three cases the interatrial shunt after the procedure was slight or absent.

The safety and long term effectiveness of the procedure need further assessment. But the potential advantages of this technique over conventional surgical valvotomy are shorter hospital admission, lower cost, and perhaps less morbidity.

References

1 Mullin EM, Glancy DI, Higgs LM, Epstein SE. Current results of mitral operation for mitral stenosis. Clinical and hemodynamic assessments in 124 consecutive patients treated by closed commissurotomy, open commissurotomy, or valve replacement. *Circulation* 1972;**46**:298–308.

2 Heger JJ, Wann LS, Weyman AE, Dillon JC, Feigenbaum H. Long-term changes in mitral valve area after successful mitral commissurotomy. *Circulation* 1979;**59**:443–8.

3 John S, Bashi VV, Jairaj PS, *et al*. Closed mitral valvotomy: early results and long-term follow-up of 3724 consecutive patients. *Circulation* 1983;**68**:891–6.

4 Kan JS, White RI, Mitchell SE, Gardener TJ. Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary valve stenosis. *N Engl J Med* 1982;**307**:540–2.

5 Lababidi Z, Wu JR. Percutaneous balloon pulmonary valvuloplasty. *Am J Cardiol* 1983;**52**:560–2.

6 Lababidi Z, Jiunn-Ren W, Wall JT. Percutaneous balloon aortic valvuloplasty: results in 23 patients. *Am J Cardiol* 1984;**53**:194–7.

7 Inoue K, Owaki T, Nakamura T, Kitamura F, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984;**87**:394–402.

8 Lock JE, Khalilullah M, Shrivastava S, Bahl V, Keane JF. Percutaneous catheter commissurotomy in rheumatic mitral stenosis. *N Engl J Med* 1985;**313**:1515–8.

9 Al Zaibag M, Ribeiro P, Al Kasab S. Percutaneous transluminal valvotomy for rheumatic mitral stenosis using a double balloon technique [Abstract]. *Br Heart J* 1986;**55**:513.

10 Babic UU, Pejcic P, Djurisic Z, Vucinic M, Grujicic SM. Percutaneous transarterial balloon valvuloplasty for mitral valve stenosis. *Am J Cardiol* 1986;**57**:1101–4.

11 MacKay RG, Lock JE, Keane JF, Safian RD, Aroesty JM, Grossman W. Percutaneous mitral valvuloplasty in an adult patient with calcific rheumatic mitral stenosis. *J Am Coll Cardiol* 1986;7:1410–5.

12 Palacios IF, Lock JE, Keane JF, Block PC. Percutaneous transvenous balloon valvotomy in a patient with severe calcific mitral stenosis. *J Am Coll Cardiol* 1986;7:1416–9.

13 Reifart N, Nowak B, Baykut D, Bussman WD, Kaltenbach M. Experimental mitral valvuloplasty of fibrotic and calcified valves with balloon catheters [Abstract]. *J Am Coll Cardiol* 1985;5:448.

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Transposition of the great arteries: late results in adolescents and adults after the Mustard procedure

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SUMMARY A selected group of 18 patients aged 15–27 years with transposition of the great arteries and a previous Mustard procedure were evaluated to determine their functional ability and clinical state. Arrhythmias were common, occurring at some time in 16/18 (89%). Arrhythmia was serious in four; two of them required pacing and two had cardiac arrests, one resulting in death. Seven (41%) had right ventricular dysfunction; this was progressive in three. Tricuspid regurgitation was present in seven (41%); it occurred in patients with normal and reduced right ventricular ejection fractions. Regurgitation became progressively worse as the right ventricle dilated. Left ventricular function was well preserved in most patients.

Fourteen (82%) of this pioneer group were leading normal lives (ability index 1 or 2). Although these results are acceptable concern remains about the probability of deteriorating right ventricular function.

The introduction of an intra-atrial baffle repair for transposition of the great arteries (the Mustard procedure) in 1964[1] dramatically changed the prognosis of babies born with this anomaly. Concern about the long term results remains, particularly the capacity of the tricuspid valve and right ventricle to support systemic pressure for many years. Much has been written about the short and medium term results of the Mustard procedure, but little is known about the long term functional ability of these patients when they become adults. We evaluated a selected group of survivors who reached adulthood after the Mustard procedure.

Patients and methods

We studied all patients with angiographically proven transposition of the great arteries and a previous Mustard operation who were seen at the National Heart Hospital, London, since 1965 and who survived beyond the age of 14 years. All patients were referred from the Hospital for Sick Children in London. There were 18 patients aged 15–27 years (mean 20) who had had a Mustard operation when they were five months to 11 years old; one patient has died. Table 1 shows the clinical data. Eleven patients (61%) had had a Blalock-Hanlon septectomy at nine days to six years and six patients had had a Rashkind atrial septostomy. Three patients required ligation of a ductus arteriosus (cases 10, 12, and 16), three had closure of a ventricular septal defect (cases 10, 14, and 16), and one had a pulmonary artery banding (case 10). The 17 living patients were seen in 1986 (mean follow up 18 years) and had clinical examination, chest *x* ray, electrocardiogram, cross sectional echocardiogram, exercise test using the modified Bruce protocol, and 24 hours of ambulatory electrocardiography. Left and right ventricular ejection fractions were measured by equilibrium electrocardiogram gated radionuclide angiography. The ability index[2] was assessed in each patient to evaluate their quality of life. Seven had cardiac catheterisation after operation; in three this was because of deteriorating haemodynamic function.

Results

One patient (case 18, aged 15) who had cardiomegaly and heart failure for three years died in a disco. He had had episodes of atrial fibrillation and flutter from the age of three and despite four cardioversions

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Table 1 *Clinical data on 18 patients aged > 14 years with transposition of the great arteries and a Mustard operation*

Case	*Age in 1987*	*Age at Mustard*	*Year*	*Previous operations*	*Age*	*Ability index*	*Exercise test (Bruce)*	*LVEF (%)*	*RVEF (%)*	*Basic rhythm*	*Complications*
Alive:											
1	27	6 yr	1965	Blalock-Hanlon	9 days	1	Stage IV	60	26	SR	R hemiplegia
2	26	6 yr	1966	Blalock-Hanlon	2 mnth	1	Stage IV	59	53	Junctional	Mild MR, TR
3	26	11 yr	1971	Blalock-Hanlon	6 yr	2	Stage III	50	30	SR	—
4	25	6 yr	1965	Blalock-Hanlon	2 mnth	1	Stage IV	57	43	SR	—
5	25	5 yr	1966			3	Stage II	25	27	SR	RVF, severe PHT, severe TR
6	22	4 yr	1967	Blalock-Hanlon	10 mnth	1	Stage IV	75	55	Junctional	"Sudden death", severe LVOTO
7	21	14 mnth	1966	Blalock-Hanlon	1 yr	3	Stage III	48	24	Paced	RVF, severe TR
8	20	5 yr	1971	Blalock-Hanlon	2 mnth	2	Stage III	55	45	Junctional	—
9	20	17 mnth	1967	Blalock-Hanlon	7 weeks	1	Stage IV	51	35	Junctional	Mild TR
10	20	3 yr*	1967	Blalock-Hanlon + ligation of DA + banding of PA	9 mnth	2	Stage III	66	48	SR	—
11	19	2 yr	1969	Rashkind	9 days	1	Stage IV	57	36	SR	R hemiplegia, epilepsy
12	18	22 mnth 7 yr	1969 1974	(+ ligation of DA) (obstructed venous inflow)		1	Stage III	77	43	SR	Epilepsy Mild TR
13	18	13 mnth	1969	Rashkind	3 weeks	1	Stage IV	46	30	SR	—
14	17	6 yr*	1974	Rashkind Blalock-Hanlon	6 days 2 yr	1	Stage IV	43	25	SR	LVOTO
15	17	7 mnth	1970	Rashkind	3 mnth	1	Stage V	61	44	SR	Mild TR
16	15	10 mnth*	1970	Rashkind + ligation of DA	2 mnth	3	Stage II	30	17	Junctional	RVF, severe PHT, severe TR
17	15	5 mnth 7 yr	1972 1978	Rashkind (obstructed venous inflow)	2 days	1	Stage IV	40	50	Junctional	—
Dead:											
18	15	22 mnth	1966	Blalock-Hanlon	4 mnth					Atrial flutter/ fibrillation	RVF, cardioversions × 4, sudden death

*Closure of ventricular septal defect

DA, ductus arteriosus; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation, PA, pulmonary artery; PHT, pulmonary hypertension; R, right; RVEF, right ventricular ejection fraction; RVF, right ventricular failure, SR, sinus rhythm; TR, tricuspid regurgitation.

did not maintain sinus rhythm. He also had episodes of nodal rhythm with rates of 45 beats per minute during sleep. Quinidine had been stopped a month before he died when his ability index was 3.

ABILITY INDEX AND EXERCISE CAPACITY

Fourteen of the 17 patients have an ability index of 1 or 2 and are either working or are at school or college. One (case 4) had an uncomplicated pregnancy and has a normal three year old son. Three patients (cases 5, 7, and 16) have deteriorated from ability indices of 2 to 3 in the past year because of right ventricular failure and tricuspid regurgitation. Figure 1 shows the ability index and exercise capacity of 17 patients.

Most patients (10/17 (59%)) reached at least stage IV of the modified Bruce protocol and stopped because of shortness of breath or fatigue. No one stopped exercise because of arrhythmia. The two most severely limited patients (cases 5 and 16) could not complete stage II of the exercise test. Both have considerable impairment of right ventricular function and pulmonary hypertension. The ability index of each patient correlated approximately with the

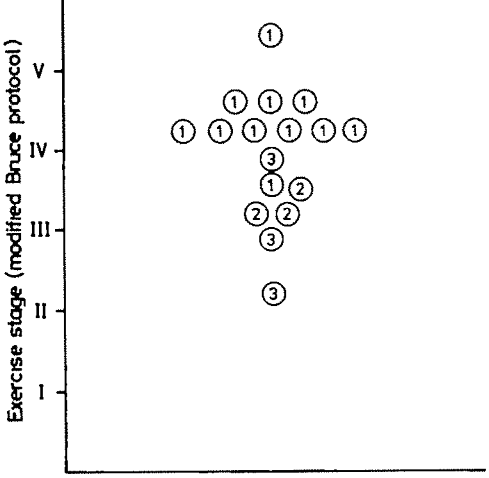

Fig 1 *Exercise capacity on the treadmill of 17 adults after the Mustard procedure. The ability index of each patient is shown. Grade 1 = normal life with full time work; grade 2 = able to do part time work, life modified by symptoms; grade 3 = unable to work, limited activities; grade 4 = extreme limitation, dependent.*

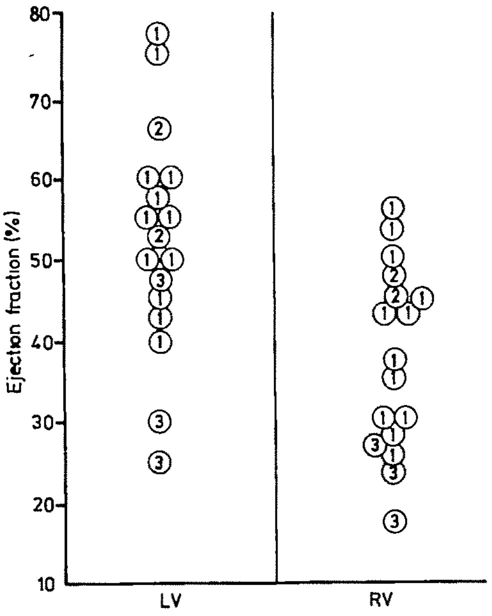

Fig 2 *Ventricular ejection fractions, measured by radionuclide angiography, of 17 adults after the Mustard procedure. The ability index of each patient is shown within the circles. LV, left ventricle; RV, right ventricle.*

exercise capacity on formal testing. Two patients (cases 1 and 11) had hemiplegia which dated from the time of the Mustard operation, and two patients (cases 11 and 12) had epilepsy.

HAEMODYNAMIC AND VENTRICULAR FUNCTION

Figure 2 shows the left and right ventricular ejection fractions measured by radionuclide angiography. Seven (41%) of 17 patients have impaired (<35%) right ventricular ejection fractions (cases 1, 3, 5, 7, 13, 14, and 16); only three (cases 5, 7, and 16) have symptoms. In all of them progressive right ventricular failure developed in the past year when they were 15, 20, and 24 years old. Tricuspid regurgitation was moderate to severe in all three and obviously progressive in two.

Patient 7 was first seen at the National Heart Hospital in 1983, aged 18, when he had an ability index of 2 and a cardiothoracic ratio of 0·59. He had atrial flutter after his Mustard operation in 1966, and required an epicardial pacemaker in 1980 when the ventricular rate fell to 40/min. Five years later increasing dyspnoea developed and he needed diuretics; his cardiothoracic ratio had risen to 0·64. Investigation showed a pulmonary artery pressure of 40/16 mm Hg with a dilated right ventricle (ejection fraction 24%) and important tricuspid regurgitation.

Symptomatic right ventricular failure in patients 5 and 16 was associated with severe pulmonary hypertension of different aetiologies. Patient 5, the only patient to have neither a septostomy nor a septectomy, had a Mustard operation when he was five years old. Preoperative pulmonary artery pressure was 24/8 mm Hg and was the same four years later when mild tricuspid regurgitation with good right ventricular function was demonstrated angiographically. At the age of 19 he had an ability index of 2 with mild dyspnoea and an episode of atrial flutter; a murmur of tricuspid regurgitation remained and the cardiothoracic ratio was 0·50 (fig 3a). He returned five years later (1985) with cardiomegaly and tricuspid regurgitation which worsened over the next year giving him an ability index of 3 and a cardiothoracic ratio of 0·73 (fig 3b). The right ventricular ejection fraction had fallen to 27%. Cardiac catheterisation showed a grossly dilated, poorly contracting right ventricle with severe tricuspid regurgitation.

Patient 16 had a duct ligated at two months, and at the age of 10 months, before his Mustard operation, he had a pulmonary artery pressure of 80/40 mm Hg and a calculated pulmonary vascular resistance which was 50% of systemic. At the time of the Mustard procedure a slit-like ventricular septal defect was closed through the tricuspid valve, but before surgical closure both ventricular pressures were equal. When he was seen at age 15 years the right ventricular ejection fraction was 17%, the ventricular septal defect was open, there was severe tricuspid regurgitation, and his pulmonary artery pressure was equal to systemic pressure.

The right ventricular ejection fractions of the other four patients with asymptomatic right ventricular impairment ranged from 25% to 30%.

Four other patients (cases 2, 9, 12, and 15) have mild tricuspid regurgitation; three (cases 2, 12, and 15) have good right ventricular function and the other has a right ventricular ejection fraction which is at the lower limit of normal (35%). Thus 10 of 17 patients have normal right ventricular ejection fractions and four of them have established tricuspid regurgitation; in two (cases 12 and 15) it has developed in the last year with progressive dilatation of the right ventricle.

Left ventricular ejection fractions were normal (>45%) in 13 (76%) patients. Four patients (cases 5, 14, 16, and 17), two (14 and 16) with a ventricular septal defect, have impaired left ventricular ejection fractions. The worst affected (cases 5 and 16) with ejection fractions of 25% and 30% have severe pulmonary hypertension. The other two patients have

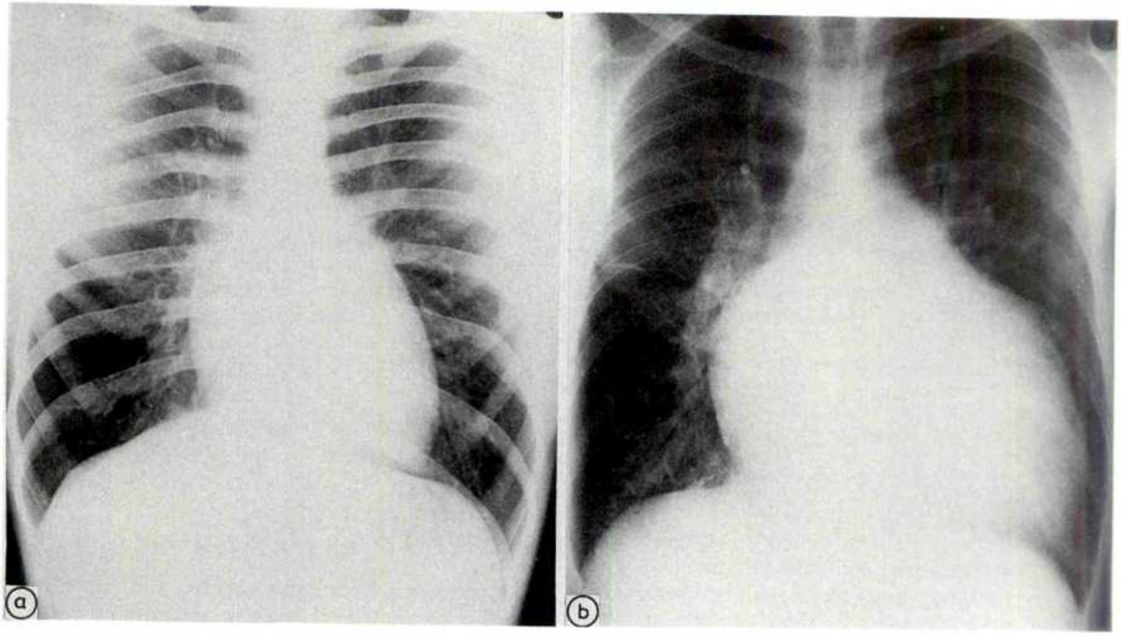

Fig 3 *(a) Chest radiograph of patient 5 at 19 years of age. At this time he had mild tricuspid regurgitation and an ability index of 2. His cardiothoracic ratio was 50%. (b) Chest radiograph six years later when he had severe tricuspid regurgitation and an ability index of 3. His cardiothoracic ratio was 73%.*

only mild impairment of left ventricular ejection fraction (43% and 40%); one (case 17) required a second bypass to refashion the atrial baffle six years after the original procedure, and at the time of the Mustard operation patient 14 required closure of a ventricular septal defect and resection of a thick fibrous ridge of tissue that was obstructing the left ventricular outflow tract and producing a gradient of 70 mm Hg. She shows slight residual subvalvar obstruction on cross sectional echocardiography but is symptom free. She has not been recatheterised. The left ventricular outflow tract was obstructed in two patients in this series. The other patient (case 6) with a left ventricular systolic gradient of 75 mm Hg at rest becomes hypotensive with the onset of supraventricular tachycardia but is symptom free in sinus rhythm. He had a gradient of 60 mm Hg across the left ventricular outflow tract before his Mustard operation, but at operation this was not thought severe enough to warrant resection. His obstruction appears to be caused mainly by the interventricular septum which bulges markedly to the left and encroaches on the outflow tract.

Four patients (cases 10, 12, 13, and 17) had obstruction of the systemic venous inflow detected at cardiac catheterisation; two had facial oedema (cases 12 and 17) and needed refashioning of the Mustard operation five and six years after the original operation. The other two have no clinical evidence of caval obstruction. No patient had pulmonary venous obstruction.

ARRHYTHMIAS

In all patients sinus rhythm was confirmed before the Mustard operation by the routine electrocardiogram. Figure 4 summarises the results of the current electrocardiograms and of the 24 hour ambulatory electrocardiograms and table 2 shows the changes in the electrocardiograms on exercise and Holter monitoring for each patient. Ten (59%) of the 17 patients were in sinus rhythm when the resting electrocardiogram was measured, six were in junctional rhythm, and one was paced (case 7) by an epicardial pacemaker implanted for atrial flutter with block 13 years after the Mustard operation. Abnormalities of rhythm were more often seen on Holter monitoring than on the routine electrocardiograms. Only two (cases 10 and 15) of the 10 patients in sinus rhythm at rest maintained this rhythm throughout the monitoring period. Sinus node dysfunction was the most common abnormality. The criteria for sinus node dysfunction were: (*a*) sinus bradycardia (heart rate <50 beats/minute during the day or <40 beats/minute during the night); (*b*) sinus pause >2 seconds; or (*c*) sinus node default leading to junctional rhythm or ectopic atrial

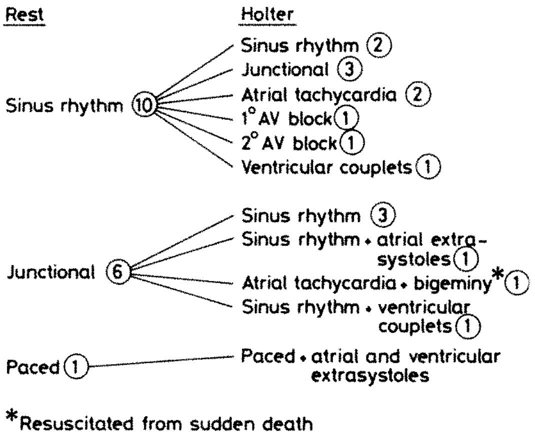
Rest
Holter
Sinus rhythm ⑩
Sinus rhythm ②
Junctional ③
Atrial tachycardia ②
1°AV block①
2°AV block①
Ventricular couplets①
Junctional ⑥
Sinus rhythm ③
Sinus rhythm + atrial extra-systoles①
Atrial tachycardia + bigeminy*①
Sinus rhythm + ventricular couplets①
Paced①
Paced + atrial and ventricular extrasystoles
*Resuscitated from sudden death

Fig 4 *Summary of resting and Holter electrocardiograms of 17 adults after the Mustard procedure. AV, atrioventricular.*

rhythm. It was present in 10 (59%) of the 17 survivors. Some patients had combinations of sinus node dysfunction and atrial and/or ventricular ectopic complexes (table 2); some of these arrhythmias were evident on exercise testing. Atrioventricular block was present at some time in three patients (cases 6, 11, and 14). It was first degree in two and second degree in one.

Five of the six patients with junctional rhythm at rest went into sinus rhythm on exercise (cases 2, 6, 8, 17, and 19). Junctional rhythm occurred at some time in 11 patients, but junctional bradycardia (<40 beats/minute) was found in only three (cases 2, 4, and 8). Patient 2 with the tachy/bradycardia syndrome had sinus arrest for five seconds and was paced, and patients 4 and 8 have bradycardias during sleep (<34 beats/minute) but return to sinus rhythm on exercise. Both are regularly monitored. One other patient was paced because of atrial flutter and a slow ventricular response.

One patient (case 6) was resuscitated from "sudden death". Before this he was in stable junctional rhythm. Electrophysiological study demonstrated a rapid supraventricular tachycardia associated with profound hypotension, probably contributed to by an associated left ventricular outflow tract obstruction. He has remained free of tachycardia for one and a half years on digoxin and disopyramide.

Although few patients showed ectopy on the routine electrocardiogram, nine patients showed atrial or ventricular ectopy or both on exercise testing or Holter monitoring.

Discussion

This series was selected by survival and referral and does not necessarily reflect the results of all patients after the Mustard procedure. Patients were operated on at the Hospital for Sick Children between 1965 and 1974 and should be regarded as a pioneer group. Between 1965 and 1971, 200 patients had the Mustard operation in that unit,[3] but we do not know the long term fate of the other patients. Referral to our unit was by consultant preference.

This study was undertaken to determine the problems faced by adult survivors. The mean follow up is probably the longest of any published report.

Table 2 *Electrocardiograms at rest, on exercise, and on Holter monitoring in 17 patients after a Mustard operation*

Case	*Resting ECG*	*Exercise*	*Holter*
1	SR	SR, occasional unifocal VPCs	Junctional-triplet (idioventricular escape)
2	Junctional, RBBB, L post hemiblock	SR, RBBB	Junctional bradycardia, atrial fibrillation, sinus arrest (5 s)
3	SR, RBBB	SR, occasional VPCs, occasional APCs	APCs (multifocal atrial tachycardia), SVT, junctional rhythm, VPCs
4	SR	SR, occasional APCs	APCs (unifocal), sinus arrest (2 s), junctional bradycardia
5	SR, RBBB	Junctional, APCs (unifocal), VPCs (bigeminy)	Atrial tachycardia, with 2:1 A–V block
6	Junctional	SR, occasional VPCs, occasional APCs	APCs, VPCs, junctional, 1° A–V block
7	Paced (flutter with block)	Junctional, APCs, VPCs	VPCs, APCs
8	Junctional	SR	Junctional bradycardia, APCs (unifocal)
9	Junctional	SR	Junctional
10	SR	SR	SR
11	SR, RBBB	SR, RBBB	1° A–V block, intermittent
12	SR	VPCs (bigeminy), APCs	VPCs (bigeminy)
13	SR	SR	Junctional
14	SR	SR	2° A–V block
15	SR	SR	SR
16	Junctional, RBBB	Junctional, RBBB	Occasional SR, ventricular couplets, APCs
17	Junctional	SR	Junctional/SR

APCs, atrial premature complexes (extrasystoles); A–V, atrioventricular; L post, left posterior; RBBB, right bundle branch block; SR, sinus rhythm; SVT, supraventricular tachycardia; VPCs, ventricular premature complexes (extrasystoles).

Arrhythmias were the most common complication and they occurred at some time in 16/18 patients (89%); seven were symptomatic. The reported frequency of rhythm and conduction disturbances after the Mustard operation varies from 13% to 100%.[4-7] The high frequency in our series could in part be explained by the inclusion of some bradycardias that may occur in the normal population[8] and may also relate to the intensity of search for arrhythmias—the combination of exercise testing and Holter monitoring undoubtedly increases the yield. But more likely explanations are that many of our patients had had a Blalock-Hanlon septectomy (11/18, 61%) and the long duration of patient follow up, since the frequency of sinus rhythm decreases as patients are followed for longer periods.[9-11]

Seven patients (cases 2, 3, 5-7, 12, and 18) required intervention because of arrhythmia and, as in other studies,[6 9] tachycardia and bradycardia have been frequent. Two (cases 2 and 7) required pacing, three (cases 5, 12, and 18) needed cardioversion for atrial flutter, and two needed antiarrhythmic treatment for supraventricular tachycardia. Only one patient (case 2) needed all these treatments at different times because of the tachy/bradycardia syndrome. The arrhythmias were easy to control, with the exception of patient 18 who died of recurrent atrial fibrillation and severe right ventricular failure.

As in other studies[12] sinus node dysfunction was common (59%). It is caused either by direct damage at operation or by obliteration of the sino-atrial node artery. Previous electrophysiological studies showed a slow pacemaker recovery time after the Mustard procedure, with the junctional area sometimes recovering before the sinus node.[13] The absence of intra-atrial, atrioventricular, and His-Purkinje conduction abnormalities[14] also suggests that sinus node damage is the main cause of arrhythmias in these patients.

It is surprising that five of the six with junctional rhythm at rest developed sinus rhythm on exercise, but this finding should not be considered reassuring since one patient (case 2), who had been in junctional rhythm for 10 years and symptom free, developed bradycardia and sinus arrest with dizziness and required pacing.

Although no continuous arrhythmias were provoked by exercise, ventricular extrasystoles were provoked in six and were seen on the Holter recordings in six. None had ventricular tachycardia, but it may develop later. Ventricular tachycardia is a recognised cause of morbidity after the Mustard operation, and previous studies have demonstrated multiple ventricular extrasystoles in 12-40% of patients after this operation.[5 10] Thus, although collapse and sudden death late after the Mustard procedure have been associated with atrioventricular conduction abnormalities,[7] tachycardia, either supraventricular or ventricular, may be equally important; as shown by patient 6 who was resuscitated from "sudden death". Both exercise testing and Holter monitoring should be performed annually in Mustard patients to detect potentially life threatening arrhythmias. Previous reports have suggested that arrhythmias are more common in those who have a more complicated surgical repair (closure of a ventricular septal defect or resection of subpulmonary stenosis)[6] but in this series no such relation was shown.

Right ventricular dysfunction is a well recognised complication of the Mustard procedure; however, it may be present before operation. It is thought to occur because the structure and contraction pattern of the right ventricle are often abnormal and the ventricle is additionally stressed by having to support systemic pressure.[15] We found a high frequency (41%) of reduced right ventricular ejection fraction in our patients. It caused symptoms in three who have associated tricuspid regurgitation. The development of right ventricular failure was not predictable; of the three symptomatic patients, one with a ventricular septal defect developed failure at 15 years and the other two (cases 5 and 7) developed failure at 25 and 21 years respectively. Patient 5 had had a normal cardiothoracic ratio five years before although he did have established tricuspid regurgitation. There was a possible explanation for reduced right ventricular ejection fractions in five of the seven patients in whom this feature was found—two had had a ventricular septal defect closed and three had had the Mustard operation performed when they were more than five years old. The other two had the operation performed when they were less than 14 months old. Ventricular septal defects are known to be associated with impaired ventricular function[15]; two of the three who had a ventricular septal defect had reduced right ventricular ejection fractions. Preoperative damage from hypoxia may also contribute to right ventricular dysfunction, which would suggest that patients undergoing the Mustard operation later in life would be more susceptible to right ventricular dysfunction. This suggestion was not borne out by this study, in which only three patients (cases 15-17) had the operation in infancy.

Tricuspid regurgitation was found in seven (41%); four of them had normal right ventricular ejection fractions. In two patients (cases 12 and 15) tricuspid regurgitation was detected by Doppler within the last year and was associated with right ventricular dilatation seen on cross sectional echocardiography. Tricuspid regurgitation occurs pari passu with right ventricular dilatation, as the tricuspid valve ring stretches and the leaflets fail to coapt. Initially the ejection fractions are preserved. No one had tricuspid regurgitation secondary to ruptured chordae or endocarditis. Previous reports have suggested that severe tricuspid regurgitation and right ventricular dysfunction are commonly related to surgical closure of a ventricular septal defect through the tricuspid valve[16 17]; only one of our three patients who had a ventricular septal defect closed has tricuspid regurgitation.

The management of patients who develop right ventricular failure and tricuspid regurgitation late after the Mustard procedure is difficult. Tricuspid valve replacement in the presence of severe right ventricular failure carries a high risk. Other treatment options include cardiac transplantation or a two stage procedure with banding the pulmonary artery to "retrain" the left ventricle, followed by an arterial switch and take down of the atrial baffle. Early results appear to be satisfactory,[18] provided that pulmonary artery banding is performed when diuretics become necessary.

Left ventricular ejection fractions were normal in 13/17 patients (76%); two of the four with impaired function (one with pulmonary hypertension) had closure of a ventricular septal defect at the time of the Mustard procedure, and closure has been a recognised association in other studies.[14] Pulmonary hypertension resulting not from a ventricular septal defect but from tricuspid regurgitation probably causes left ventricular dysfunction in one other patient.

Obstruction of the left ventricular outflow tract was uncommon in this series and only caused symptoms when it was associated with a tachycardia. Obstruction did not appear to progress. Obstruction of the superior vena cava was also uncommon (17%); all three patients with this feature had collateral venous channels demonstrated on angiography, but the presence of collaterals does not preclude clinical symptoms.[17] We have no evidence that caval obstruction recurs late after initial relief.

Most late survivors (14/17, 82%) lead normal lives and have a good exercise capacity, although abnormal ventricular ejection fraction responses to exercise have been found in some long term survivors of the Mustard procedure, suggesting a decrease in myocardial reserve.[19]

These results in selected patients illustrate some of the problems which may be faced by adults with transposition treated by intra-atrial baffle procedures. Practices have changed since these patients had their operations and intra-atrial switch procedures are now usually performed in infancy and arterial switch operations during the neonatal period. Thus in the future problems may be different. Most of this pioneer group have survived into their twenties and lead normal active lives. But we remain concerned about the long term function of the right ventricle in these patients.

Mr J Stark, Mr M de Leval, the late Mr D Waterston, and the late Mr E Aberdeen successfully operated on these patients. We thank Dr R Bonham Carter, Dr J Taylor, Professor F Macartney, and Dr A Hollman for referring these patients for long term care.

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References

1 Mustard WT. Successful two-stage correction of transposition of the great vessels. *Surgery* 1964;55: 469–72.

2 Warnes CA, Somerville J. Tricuspid atresia in adolescents and adults: current state and late complications. *Br Heart J* 1986;56:535–43.

3 Breckenridge IM, Oelert H, Stark J, Graham GR, Bonham-Carter RE, Waterston DJ. Mustard's operation for transposition of the great arteries. *Lancet* 1972;i:1140–2.

4 Clarkson PM, Barratt Boyes BG, Neutze JM. Late dysrhythmias and disturbances of conduction following Mustard operation for complete transposition of the great arteries. *Circulation* 1976;53:519–24.

5 Saalouke MG, Rios J, Perry LW, Shapiro SR, Scott LP. Electrophysiologic studies after Mustard's operation for d-transposition of the great vessels. *Am J Cardiol* 1978;41:1104–9.

6 Southall DP, Keeton BR, Leanage R, *et al.* Cardiac rhythm and conduction before and after Mustard's operation for complete transposition of the great arteries. *Br Heart J* 1980;43:21–30.

7 Lewis AB, Lindesmith GG, Takahashi M, *et al.* Cardiac rhythm following the Mustard procedure for transposition of the great vessels. *J Thorac Cardiovasc Surg* 1977;73:919–26.

8 Southall DP, Johnston F, Shinebourne EA, Johnston PGB. 24-hour electrocardiographic study of heart rate and rhythm patterns in population of healthy children. *Br Heart J* 1981;45:281–91.

9 El-Said GM, Rosenberg HS, Mullins CE, Hallman GL, Cooley DA, McNamara DG. Dysrhythmias after Mustard's operation for transposition of the great arteries. *Am J Cardiol* 1972;30:526–32.

10 Hayes C, Boxer RA, Krongrad E, Gersony WM. Cardiac rhythm after the Mustard operation for transposition of the great arteries [Abstract]. *Am J Cardiol* 1980;45:430.

11 Hayes CG, Gersony WM. Arrhythmias after the Mustard operation for transposition of the great arteries: a long term study. *J Am Coll Cardiol* 1986;7:133–7.

12 Beerman LB, Neches WH, Fricker FJ, *et al.* Arrhyth-

mias in transposition of the great arteries after the Mustard operation. *Am J Cardiol* 1983;51:1530–4.

13 El-Said GM, Gillette PC, Mullins CE, Nihill MR, McNamara DG. Significance of pacemaker recovery time after the Mustard operation for transposition of the great arteries. *Am J Cardiol* 1976;38:448–51.

14 Gillette PC, El-Said GM, Sivarajan N, Mullins CE, Williams RL, McNamara DG. Electrophysiological abnormalities after Mustard's operation for transposition of the great arteries. *Br Heart J* 1974;36:186–91.

15 Hagler DJ, Ritter DG, Mair DD, *et al.* Right and left ventricular function after the Mustard procedure in transposition of the great arteries. *Am J Cardiol* 1979;44:276–83.

16 Godman MJ, Friedli B, Pasternac A, Kidd BSL, Trusler GA, Mustard WT. Hemodynamic studies in children four to ten years after the Mustard operation for transposition of the great arteries *Circulation* 1976;53:532–8.

17 Park SC, Neches WH, Mathews RA, *et al.* Hemodynamic function after the Mustard operation for transposition of the great arteries. *Am J Cardiol* 1983;51:1514–9.

18 Mee RBB. Severe right ventricular failure after Mustard or Senning operation. *J Thorac Cardiovasc Surg* 1986;92:385–90.

19 Murphy JH, Barlai-Kovach MM, Mathews RA, *et al.* Rest and exercise right and left ventricular function late after the Mustard operation: assessment by radionuclide ventriculography. *Am J Cardiol* 1983;51:1520–5.

Br Heart J 1987;58:156–61

Dilated cardiomyopathy: diagnostic accuracy of endomyocardial biopsy

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SUMMARY A histopathological index of contractility failure, which was reported to be accurate for the diagnosis of idiopathic dilated or congestive cardiomyopathy in Japan, was used to assess endomyocardial biopsy specimens from 41 Dutch patients with suspected dilated cardiomyopathy. The calculated index had a sensitivity of 62·5% and a specificity of 68% for idiopathic dilated or congestive cardiomyopathy. These disappointing results indicate that the histopathological index of contractility failure does not reliably distinguish between idiopathic dilated cardiomyopathy and other diseases that cause congestive heart failure.

It is a matter of debate whether or not endomyocardial biopsy specimens should be used for the diagnosis and management of patients with idiopathic dilated (congestive) cardiomopathy.[1–3] The criteria set by the WHO/ISFC task force define the term "dilated cardiomyopathy" as a heart muscle disease of obscure origin with dilation of the ventricles.[4] Decreased myocardial contractility is the prime mechanical disorder.[5] The histopathological findings, such as myocyte hypertrophy, degeneration, interstitial fibrosis, and endocardial proliferative changes, are in themselves non-specific.[6–9] The major contribution of an endomyocardial biopsy specimen, therefore, is to rule out other conditions that can cause congestive heart failure, such as idiopathic myocarditis.[10] The existence of a relation between the features of endomyocardial biopsy specimens and prognosis is also controversial. Some workers found that prognosis was poor when myocardial fibrosis was widespread,[7 11] but others did not find such a clear correlation between light microscopical and ultrastructural findings and the course of the disease.[8 12 13] An important reason for this discrepancy may be variation in the time of biopsy in relation to the stage of the disease. Biopsy specimens are usually taken after the onset of signs and symptoms and, hence, in most instances late in the course of the myocardial disease process. Indeed, inflammatory cell reactions were more common in those patients in whom the biopsy specimen was obtained early in the disease process.[14 15] This led to the assumption that idiopathic dilated cardiomyopathy may represent the end stage of a previous myocarditis.[16]

In view of these almost universally accepted findings it is surprising that Sekiguchi *et al* and Hiroe have claimed to have established histopathological criteria that enable them accurately to diagnose dilated cardiomyopathy on endomyocardial biopsy specimens irrespective of the stage of the disease.[17–19] Sekiguchi *et al* and Hiroe have worked out a histopathological index of the failure of contractility, which they claim is a highly specific and sensitive method for the diagnosis of idiopathic dilated (congestive) cardiomyopathy.

Because this approach does not appear to have been evaluated outside Japan we used the Japanese criteria to study a series of endomyocardial biopsy specimens taken from patients in whom the initial clinical diagnosis was idiopathic dilated cardiomyopathy.

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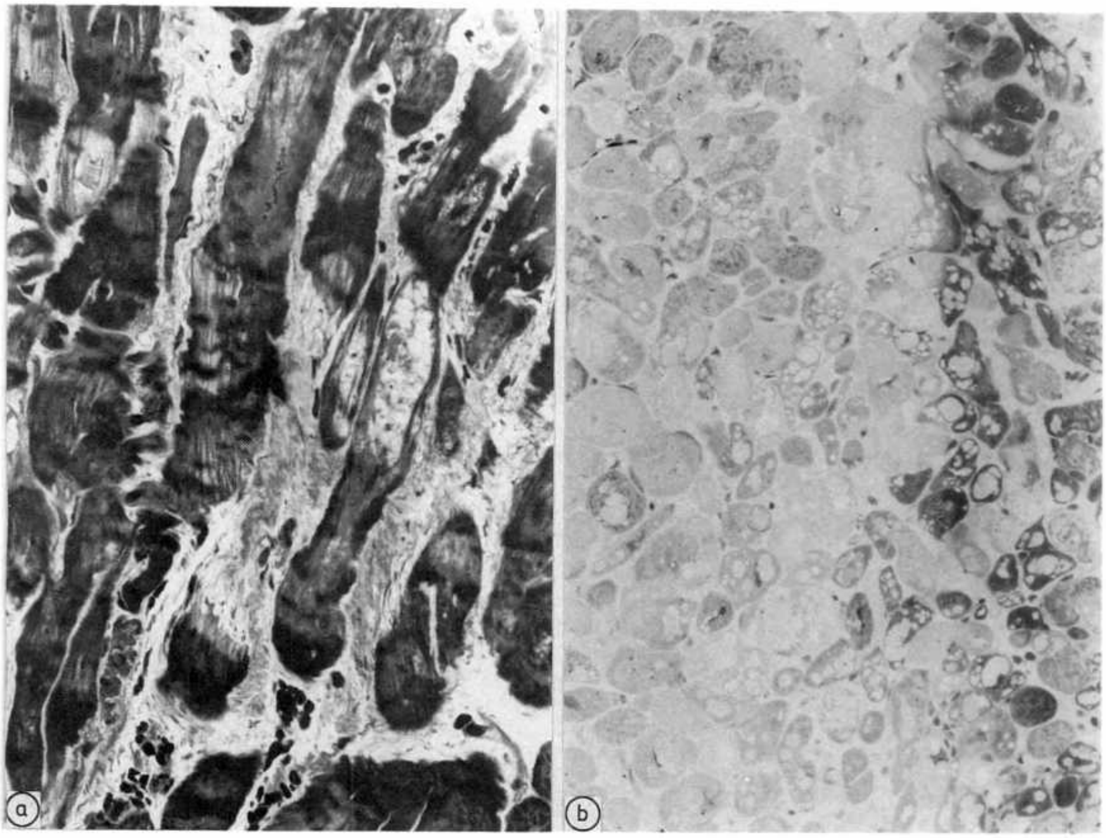

Fig 1 *Photomicrographs of endocardial biopsy specimens from patients with idiopathic dilated cardiomyopathy showing degeneration and lysis of myocytes as defined by Sekiguchi et al*[17 18] *and Hiroe.*[19] *Note the abundance of contraction bands, which are an artefact related to the procedure. (a) Mild (+) cytoplasmic vacuolisation with mild interstitial fibrosis. (b) Severe lysis (+ + +). The differences in staining intensity are related to embedding of the tissue in plastic. Ultrastructural studies showed ischaemic changes with otherwise well preserved cellular organelles. Toluidine blue stain. (original magnification a, × 140; b, × 64).*

Patients and methods

ENDOMYOCARDIAL BIOPSY SPECIMENS

We studied 41 patients (34 men and 7 women; aged 18–76, mean 42 years) in whom the initial clinical diagnosis was idiopathic dilated (congestive) cardiomyopathy. We studied a mean of five biopsy specimens from each patient; all were taken from the left ventricle. The specimens were fixed immediately in 2·5% phosphate buffered (pH 7·35) glutaraldehyde and embedded in epon. Sections 0·5 μm thick were cut and stained with an alkaline toluidine blue solution.

HISTOLOGICAL ASSESSMENT

The histological index of the failure of contractility was assessed according to Sekiguchi *et al*[17 18] and Hiroe.[19] We followed the criteria set by the Japanese workers as accurately as possible; but this does not imply that we agree with their interpretation of the various histological and cytological features.

The index is based on three pathological features: degeneration and lysis of myocytes, interstitial fibrosis, and fragmentation of muscle bundles. Each of these histological features was scored from 0 to 3 (figs 1–3). The index was calculated by adding the score for each of the three histological features.

In addition, attention was given to attenuation of myocytes, smooth muscle cell hyperplasia in the endocardium, and changes in small vessels. The histological analysis was performed without knowledge of the clinical diagnosis.

CLINICAL DIAGNOSIS

The table shows the definitive diagnoses in 41 patients with an initial clinical diagnosis of idio-

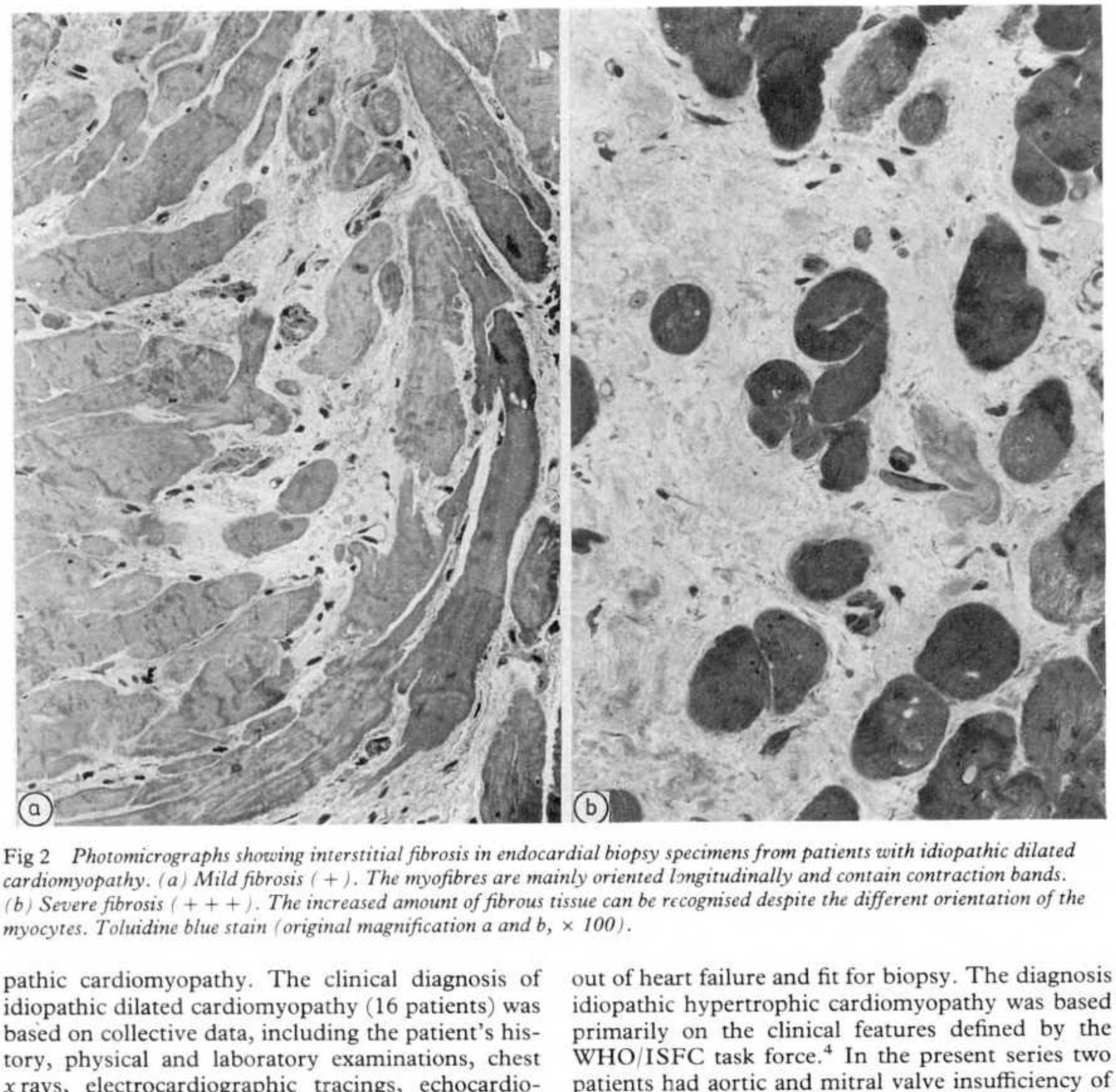

Fig 2 *Photomicrographs showing interstitial fibrosis in endocardial biopsy specimens from patients with idiopathic dilated cardiomyopathy. (a) Mild fibrosis (+). The myofibres are mainly oriented longitudinally and contain contraction bands. (b) Severe fibrosis (+++). The increased amount of fibrous tissue can be recognised despite the different orientation of the myocytes. Toluidine blue stain (original magnification a and b, × 100).*

pathic cardiomyopathy. The clinical diagnosis of idiopathic dilated cardiomyopathy (16 patients) was based on collective data, including the patient's history, physical and laboratory examinations, chest *x* rays, electrocardiographic tracings, echocardiography, radionuclide imaging, and cardiac catheterisation, including selective coronary arteriography. In each instance the clinical signs had been present for over six months and the patients all out of heart failure and fit for biopsy. The diagnosis idiopathic hypertrophic cardiomyopathy was based primarily on the clinical features defined by the WHO/ISFC task force.[4] In the present series two patients had aortic and mitral valve insufficiency of uncertain origin. The six patients in the miscellaneous group had various conditions, such as rheumatoid heart disease, lymphoblastic leukaemia, acquired immune deficiency syndrome, and no cardiac abnormalities.

Table *Definitive clinical diagnoses*

Idiopathic dilated cardiomyopathy	16
Idiopathic hypertrophic cardiomyopathy (HCM)	5
Arrhythmias:	
Paroxysmal supraventricular tachycardia	2
Paroxysmal ventricular tachycardia	3
Hypertensive heart disease	5
Ischaemic heart disease	2
Valvar heart disease	2
Miscellaneous	6

Results

Hypertrophy of myocytes was seen in all 41 patients but small vessel disease and inflammatory cell infiltration were not seen in any. Attenuation of the myocytes was seen in only two of the 16 patients with idiopathic dilated cardiomyopathy. Endocardial smooth muscle cell hyperplasia was seen in six of these 16 patients and in one each of the

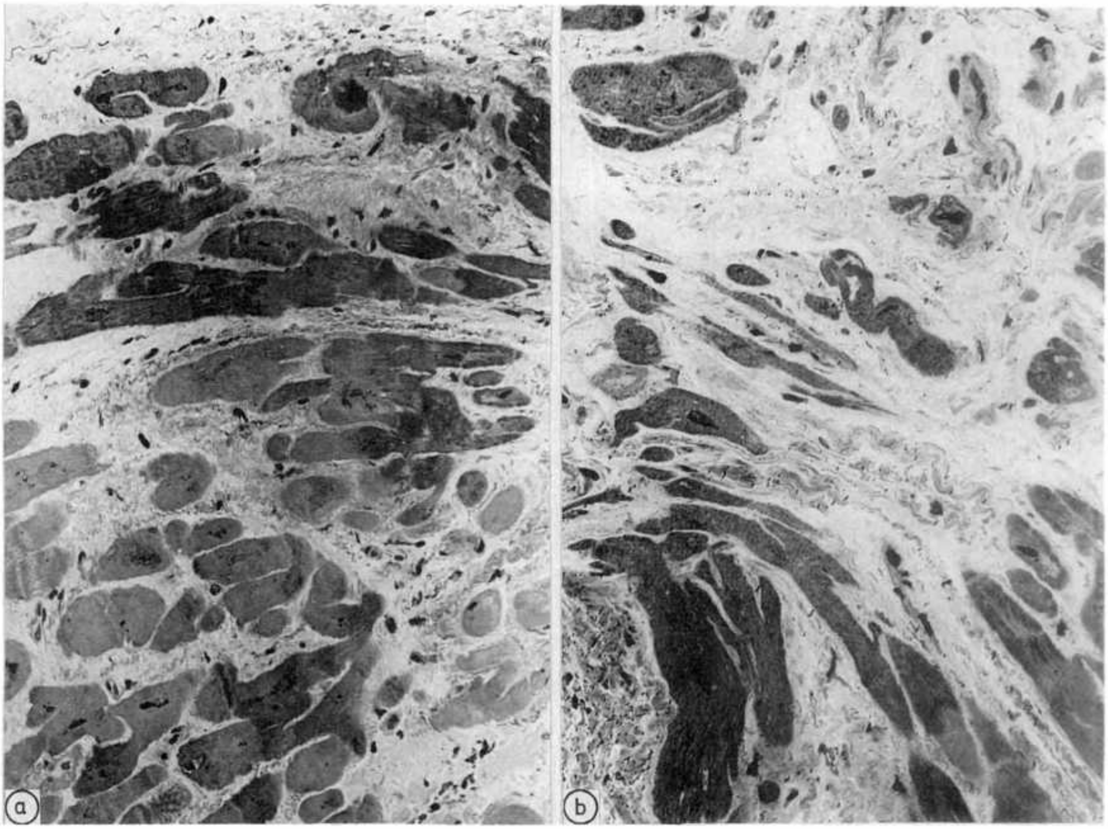

Fig 3 *Photomicrographs showing fragmentation of muscle bundles in endocardial biopsy specimens from patients with idiopathic dilated cardiomyopathy. (a) Mild (+) and (b) severe (+++). The term fragmentation includes fibres that taper out or "fragment" amidst fibrous tissue. Toluidine blue stain (original magnification a and b, × 100).*

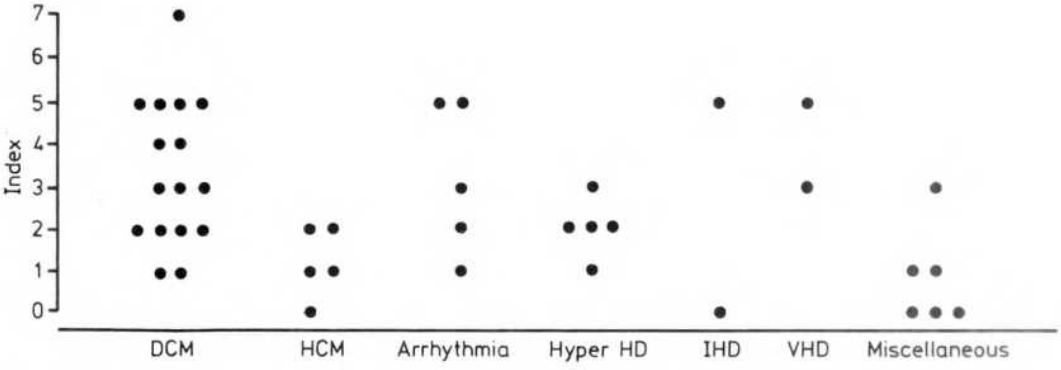

Fig 4 *Histopathological index of failure of contractility calculated from endomyocardial biopsy specimens and corresponding clinical diagnoses. DCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; Hyper HD, hypertensive heart disease; IHD, ischaemic heart disease, VHD, valvar heart disease.*

five patients with primary arrhythmias and the two patients with valvar heart disease.

Figure 4 shows the histopathological contractility failure index and the corresponding clinical diagnosis for all patients. According to Sekiguchi and coworkers a high index score is diagnostic for dilated cardiomyopathy. They use a mean (SD) value of 3·5 (1·4) as the indicator for the disease.[19] In the present study, therefore, an index score of $\geqslant 3$ is regarded as positive histological evidence of dilated cardiomyopathy.

The sensitivity and specificity of the index were as follows:

$$\text{Sensitivity} = \frac{\text{true positive}}{\text{true positive} + \text{false negative}} \times 100$$

$$= \frac{10}{10 + 6} \times 100 = 62{\cdot}5\%$$

$$\text{Specificity} = \frac{\text{true negative}}{\text{false positive} + \text{true negative}} \times 100$$

$$= \frac{17}{8 + 17} \times 100 = 68\%$$

Discussion

The diagnosis idiopathic dilated or congestive cardiomyopathy is difficult because it is based mainly on the exclusion of known causes of heart failure rather than on positive criteria. It is likely that the disease has a multifactorial origin with a final common pathway characterised by decreased myocardial contractility. From this it is understandable that the histopathology in the later stages of the disease will be non-specific and, from the point of view of diagnosis, not very helpful. Baandrup *et al* did not find a significant correlation between the histological features and the clinical diagnosis in a series of 361 endomyocardial biopsy specimens from patients with suspected cardiomyopathy.[13] Moreover, they were unable to confirm the congestive nature of the underlying heart disease on the basis of the biopsy specimens alone and concluded that biopsy specimens did not indicate the prognosis. Moreover, in a retrospective study, they found no relation between ultrastructural findings and prognosis.[20] When Breithardt and co-workers used a scoring system that resembled the one used by Baandrup *et al* they too concluded that the results of long term follow up could not be accurately established from biopsy specimens.[12] On the other hand, myocyte degeneration appeared to be a prognostically important factor in patients with a history of less than two years. More recently, Rose and Beck examined 76 endomyocardial biopsy specimens from patients with the clinical diagnosis of dilated cardiomyopathy and 54 necropsy specimens from patients with this disease.[21] They found fibrosis in only 28% of the endomyocardial biopsy specimens and in 50% of the sections obtained at necropsy. Moreover, they found remarkably little myocytolysis—none in the endomyocardial biopsy specimens and only 9% in the necropsy series. These workers also concluded that the clinical evaluation of cardiac dysfunction correlated poorly with the morphology of the myocardial tissue. The findings of Rose and Beck,[21] in particular, are in striking contrast with the observations made by Sekiguchi *et al*, who showed 100% fibrosis both in the endomyocardial biopsy specimens and in the necropsy specimens and a much higher frequency of degeneration, including myocytolysis. In fact, Sekiguchi *et al* emphasised that a semiquantitative assessment of the endomyocardial biopsy specimens predicted the outcome in patients with dilated cardiomyopathy.[17-19]

Why do workers in different parts of the world come to such divergent conclusions? We followed Sekiguchi's method as closely as possible. This was not easy because the precise criteria on how to apply the grading system from 0 to 3 for each of the key items—that is degeneration and lysis of myocytes, interstitial fibrosis, and fragmentation of muscle bundles—are not clearly stated. Moreover, identification of the histopathological features promoted by the Japanese workers is highly subjective. Another important criticism is that the changes may represent various non-specific responses to injury, such as ischaemia. For instance, the degenerative changes that they assess are for the most part myofibrillar degeneration as described by Reichenbach and Benditt[22] (fig 1a). Also vacuolar degeneration (fig 1b) is highly suggestive of subendocardial ischaemia as described by Geer *et al*.[23] The changes regarded as typical of fragmentation of myocytes may be partly the result of orientation of myocytes out of the plane of section and fibrosis. In the present study, however, these changes were categorised as "fragmentation". Despite our reservations about the histological interpretation of these features we followed the Japanese criteria as closely as possible to ensure that the two studies were comparable.

We found that histological assessment did not allow a clear and unambiguous differentiation of the various clinical subgroups or of individual patients. Nevertheless, the histopathological index was much higher in patients with dilated cardiomyopathy (3·3) than in those with hypertrophic cardiomyopathy (1·2). In patients with arrhythmia, valvar heart disease, ischaemic cardiomyopathy, and heart disease secondary to long lasting hypertension, however, the histopathological contractility failure index was in the range of that found in dilated cardiomyopathy. Moreover, when an index score of three was taken to indicate the diagnosis of dilated cardiomyopathy the sensitivity was 62·5% and the specificity was 68%.

We found that the histopathological contractility failure index was not a reliable tool in diagnosing dilated cardiomyopathy. The results suggest that the index reflects cardiac muscle damage that is not necessarily specific to idiopathic dilated cardiomyopathy. This conclusion accords with the nonspecific histological criteria of the index and the current hypothesis that dilated cardiomyopathy is not an entity in the strict sense but rather a multifactorial disease with a final common pathway leading to heart failure.

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References

1 Johnson RA, Palacios I. Dilated cardiomyopathies of the adult (first of two parts). *N Engl J Med* 1982;**307**:1051–8.

2 Johnson RA, Palacios I. Dilated cardiomyopathies of the adult (second of two parts). *N Engl J Med* 1982;**307**:1119–26.

3 Fowles RE, Mason JW. Role of cardiac biopsy in the diagnosis and management of cardiac disease. *Prog Cardiovasc Dis* 1984;**27**:153–72.

4 Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. *Br Heart J* 1980;**44**.672–3.

5 Hirota Y, Shimizu G, Kaku K, Saito T, Kawamura K. Mechanisms of compensation and decompensation in dilated cardiomyopathy. *Am J Cardiol* 1984;**54**: 1033–8.

6 Olsen EGJ. The pathology of cardiomyopathies. A critical analysis. *Am Heart J* 1979;**98**:385–92.

7 Shirey EK, Proudfit WL, Hawk WA. Primary myocardial disease. Correlation with clinical findings, angiographic and biopsy diagnosis. *Am Heart J* 1980;**99**:198–207.

8 Unverferth DV, Fetters JK, Unverferth BJ, *et al.* Human myocardial characteristics in congestive heart failure *Circulation* 1983;**68**:1194–200.

9 Davies MJ. The cardiomyopathies: a review of terminology, pathology and pathogenesis. *Histopathology* 1984;**8**·363–93.

10 Mason JW, Billingham ME, Ricci DR. Treatment of acute inflammatory myocarditis assisted by endomyocardial biopsy. *Am J Cardiol* 1980;**45**:1037–44.

11 Kunkel B, Lapp H, Kober G, Kalgenbach M. Correlations between clinical and morphologic findings and natural history in congestive cardiomyopathy. In: Kaltenbach M, Loogen F, Olsen EGJ, eds. *Cardiomyopathy and myocardial biopsy*. Berlin. Springer Verlag, 1978:271–83.

12 Breithardt G, Kuhn H, Knieriem HJ. Prognostic significance of endomyocardial biopsy in patients with congestive heart failure. In: Kaltenbach M, Loogen F, Olsen EGJ, eds. *Cardiomyopathy and myocardial biopsy*. Berlin: Springer Verlag, 1978: 258–70.

13 Baandrup U, Florio RA, Rehahn M, Richardson PJ, Olsen EGJ. Critical analysis of endomyocardial biopsies from patients suspected of having cardiomyopathy. II. Comparison of histology and clinical haemodynamic information. *Br Heart J* 1981;**45**. 487–93.

14 Fenoglio JJ, Ursell PCh, Kellogg CF, Drusin RE, Weiss MB. Diagnosis and classification of myocarditis by endomyocardial biopsy. *N Engl J Med* 1983;**308**:12–8.

15 Dec GW, Palacios IF, Fallon JT, *et al.* Active myocarditis in the spectrum of dilated cardiomyopathies. *N Engl J Med* 1985;**312**:885–90.

16 Subramanian R. The pathology of myocarditis and cardiomyopathy. In: Robinson JA, O'Connell JB, eds. *Myocarditis: precursor of cardiomyopathy*. Lexington, Massachusetts, Toronto: The Collamore Press, 1983:129–40.

17 Sekiguchi M, Hiroe M, Morimoto S, Kawagoe Y. The contribution of endomyocardial biopsy to the diagnosis and assessment of cardiomyopathies. In: Hayase S, Murao S, eds. *International congress series no 470. Proceedings of the VIII World Congress of Cardiology*. Amsterdam: Excerpta Medica, 1979:583.

18 Sekiguchi M, Hiroe M, Morimoto S. On the standardization of histopathological diagnosis and semiquantitative assessment of the endocardium obtained by endomyocardial biopsy. *Bull Heart Inst Jpn* 1979–1980:55–85.

19 Hiroe M. Evaluation of left ventricular function and prognosis in patients with idiopathic cardiomyopathy in comparison with endomyocardial biopsy findings with semiquantitative histopathological analysis—comparative study of hypertrophic and congestive (dilated) cardiomyopathy. [In Japanese] *J Tokyo Wom Med Coll* 1982;**52**:292–306.

20 Baandrup U, Florio RA, Roters F, Olsen EGJ Electron microscopic investigation of endomyocardial biopsy samples in hypertrophy and cardiomyopathy. *Circulation* 1981;**63**:1289–98.

21 Rose AG, Beck W. Dilated (congestive) cardiomyopathy: a syndrome of severe cardiac dysfunction with remarkably few morphological features of myocardial damage. *Histopathology* 1985,**9**:367–79.

22 Reichenbach DD, Benditt EP. Myofibrillar degeneration. A response of the myocardial cell to injury. *Arch Pathol* 1968;**85**:189–99.

23 Geer JC, Crago CA, Little WC, Gardner LL, Bishop SP. Subendocardial ischemic myocardial lesions associated with severe coronary atherosclerosis. *Am J Pathol* 1980;**98**:663–80.

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Case reports

Successful use of a right ventricular assist device

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SUMMARY Right ventricular failure caused by myocardial infarction may be refractory to treatment designed to support the systemic ventricle. A new type of right ventricular assist device driven by an impeller pump was successfully used for 79 hours after emergency revascularisation after right coronary occlusion. Despite renal failure requiring haemofiltration the patient has now fully recovered.

Right ventricular failure due to infarction on the diaphragmatic surface is characterised by hypotension, neck vein engorgement, and heart block.[1] The addition of clinically significant infarction of the left ventricular free wall and septum may contraindicate any effort to increase the right ventricular preload and may also diminish the effectiveness of pulmonary vasodilators which are the mainstay of treatment when right ventricular failure is caused by pulmonary hypertension. Left ventricular function is also embarrassed by inadequate preload caused by insufficient blood crossing the pulmonary vasculature; if this cannot be improved by standard inotropic and vasodilator methods right ventricular assistance is required to maintain systemic perfusion. Right ventricular bypass should also relieve overdistension of the ventricle thus allowing recovery by promoting coronary blood flow to viable muscle.

We describe the successful use of a simple, cheap, and adaptable right ventricular assist device; it was used to support the failing right ventricle when inotropes, vasodilators, and an intra-aortic balloon pump had failed to maintain adequate circulation and prevent progressive acidosis. There are reports of three survivors in whom the combination of an intra-aortic balloon and a right ventricular assist device was used; but none of them had renal failure.[2-4] In the present case renal failure was treated by the addition of a haemofiltration circuit.

Case report

A 63 year old previously well woman with a history of severe unstable angina was transferred for cardiological assessment to London. Cardiac catheterisation showed moderate left ventricular function, occlusion of the anterior descending coronary artery, and 95% stenosis of a large marginal coronary artery. The right coronary had an ostial stenosis and six hours after catheterisation she suffered a large inferior infarct. Despite administration of vasodilators she continued to have rest pain. She was transferred to the Brompton Hospital three days later. On admission blood pressure was 90 mm Hg and jugular venous pressure was raised 8 cm. Chest *x* ray showed diversion of venous blood to the upper lobe; the electrocardiogram showed sinus rhythm and a large inferior infarct. Pain continued and emergency revascularisation was therefore carried out. After sternotomy the blood pressure was 80–90 mm Hg and central venous pressure was 20 mm Hg; rhythm was junctional. The right atrium was tense and immobile. Both ventricles were infarcted on their diaphragmatic surfaces. The remainder of the left ventricular free wall moved well but the right ventricle, apart from the outflow tract, was dilated and immobile but not obviously infarcted. The posterior descending, marginal, and anterior descending (internal mammary artery graft) arteries were grafted. She tolerated the procedure well and cardiopulmonary bypass was discontinued without difficulty. She was in slow junctional rhythm with blood pressure 90 mm Hg and central venous pressure 18–20 mm Hg on isoprenaline 0·03 μg/kg/min with glyceryl trinitrate infusion.

During the first six hours she was stable, but then blood pressure fell and urine output declined (fig 1). She required pacing and an increased dose of inotropes (dopamine, adrenaline, and isoprenaline) (fig 2). Over the next 12 hours central venous pressure rose from 22 to 30 mm Hg and acidosis increased despite repeated correction with bicar-

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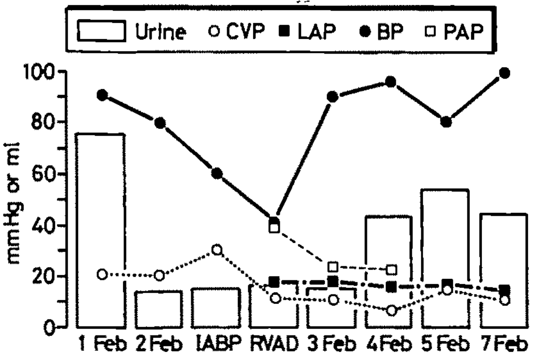

Fig 1 *Urine output, blood pressure, and pressures measured at cardiac catheterisation in a patient with right ventricular failure who was treated with a right ventricular assist device. IABP, after insertion of intra-aortic balloon pump; RVAD, after insertion of right ventricular assist device; CVP, central venous pressure (mm Hg); LAP, left atrial pressure (mm Hg); PAP, pulmonary artery pressure (mm Hg).*

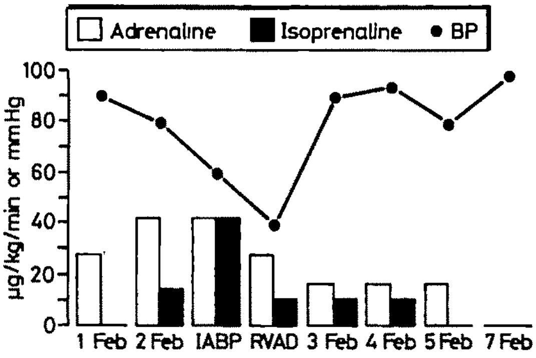

Fig 2 *Blood pressure and doses of adrenaline and isoprenaline used to treat a patient with right ventricular failure. See legend to fig 1 for abbreviations.*

bonate and insertion of an intra-aortic balloon pump. She was therefore returned to the operating theatre. External findings were similar to before. The pulmonary artery and superior vena cava were cannulated and connected percutaneously through the right hypochondrium to the right ventricular assist device and the chest was closed. The right ventricle could thus be bypassed variably. The assist device was made up of a Centrimed impeller pump without reservoir in a closed circuit. Flow was adjusted to optimise left ventricular performance: at 2 l/min left ventricular function improved dramatically with a systolic pressure of 100 mm Hg and left atrial pressure of 16 mm Hg; however, when the flow rate was further increased the left atrial pressure rose considerably and systemic blood pressure fell rapidly. Flows were therefore kept at 1–2 l/min for the next 79 hours while (fig 1) the pulmonary artery pressure steadily declined to normal (30/15 mm Hg) which was maintained when the assist device was stopped for periods of up to 60 seconds. Improvement was noticeable within 24 hours of insertion of the device and inotropic requirements declined considerably (fig 2). Partial heparinisation was maintained. The assist device was removed without difficulty 79 hours after operation. The right ventricle, apart from its diaphragmatic surface, was then seen to be beating well. The balloon pump was removed two days later.

After insertion of the assist device, renal failure (creatinine clearance 2·4 ml/min) was treated by haemofiltration with a Diafilter-20 (Amicon, Danvers, MA 01923, USA) connected in parallel with the assist device circuit. Urine output (fig 1) improved to over 30 ml/h with creatinine clearance still 2·4 ml/min. Urine osmolality rose from 308 mOsm/l to 387 mOsm/l and creatinine clearance to 16 ml/min by the twelfth day. Creatinine clearance was 48 ml/min by the 25th day and 95 ml/min on the 32nd postoperative day; creatinine clearance had peaked at 590 µmol/l.

She was extubated on the 35th day after cardiac output had been measured by thermodilution. Heart rate was 120 beats/min, central venous pressure was 15 mm Hg, right ventricular pressure 39/8 mm Hg, and pulmonary artery pressure 34/20 (mean 25) mm Hg. Cardiac output (mean of three measurements) was 4·9 l/min, systemic vascular resistance 11·4 units, pulmonary vascular resistance 1·84 units, and stroke volume 40 ml. These data indicate a highly satisfactory recovery. Echocardiography was unhelpful.

Outpatient review at five months resulted in referral for femoral artery reconstruction which was successfully performed at 10 months. Echocardiography at five months showed a normal sized right ventricular cavity and slight left ventricular enlargement with normal function.

Discussion

Right ventricular failure is often a secondary effect of left ventricular failure or other causes of pulmonary hypertension. In the case described, although the left ventricular infarct adversely affected pulmonary vascular resistance, infarction of the right ventricular diaphragmatic surface was the prime cause of right ventricular failure. Treatment was designed initially to off load the right ventricle pharmacologically and to optimise left ventricular performance. The lack of effect of balloon counterpulsation on right ventricular function confirmed the visual impression at operation that right ventricular pump failure was the main problem.

What are the options when a patient has seemingly intractable right ventricular failure? Increasing the preload on the right ventricle even further and off loading the systemic circulation can be successful; four of six patients with near normal left ventricular function survived this treatment.[1] In the present case, the right atrium was already overloaded and left ventricular function was obviously depressed; further volume loading was ineffective. Fear of terminal right ventricular overdistension prompted us to use an assist device.

In sheep and goat preparations pulmonary artery balloon counterpulsation is reported to provide some assistance to forward flow in pulmonary hypertension.[5] However, when the balloon is placed in a side arm attached to the pulmonary artery it will directly promote forward flow and this method has been used clinically and experimentally with moderate benefit.[6 7] This is slight compared with passive flow and markedly inferior to that achieved with a right ventricular pump assist device.[8]

Long term complete bypass requires full heparinisation and a membrane oxygenator, and a perfusionist must be in continuous attendance. Problems are mainly caused by progressive depletion of clotting factors and destruction of red cells and platelets. Isovolumic left ventricular contraction enhances right ventricular pump function and if the left ventricle is completely decompressed, right ventricular function declines.[9] Roller pumps may produce tubing splitting and spallation of particles within the circulation. Some of these problems occurred with extracorporeal membrane oxygenation but were overcome by centrifugal or impeller pumps with no or minimal heparinisation. Such measures should reduce the risk of bleeding, which can cause considerable mortality.[10]

In our case the right ventricle was unable to pump sufficient blood for the damaged left ventricle to perform properly. This necessitated the use of a right ventricular assist device with the patient's lungs for oxygenation. Flow rates were adjusted to "balance" the respective ventricular failures. The technique used a closed circuit and avoided the need for an oxygenator and reservoir, thereby reducing the supervision required and the possibility of accidents. We used a type of impeller pump that had not previously been used in a right ventricular assist device. Because of this low levels of heparinisation were adequate. No clots were seen when the device was removed. The system was easily adapted to the addition of a haemofiltration circuit. Disposable equipment cost approximately £380.

There is a moderately large experience in the United States with sac type ventricular assist devices, but they are expensive and scarce in the United Kingdom. Both experimental work in animals and limited clinical data suggest that pneumatic assist devices are hard to adjust to provide the low flows required. Higher flows resulted in left ventricular failure in this patient whose infarct involved the diaphragmatic wall of the left ventricle.

It is generally agreed that the device should be inserted if adequate catecholamine support and balloon counterpulsation are ineffective after a trial period of 60–120 minutes.[11 12] However, when left atrial pressure is low, aortic balloon counterpulsation is unlikely to improve right ventricular performance and this step seems unnecessary unless left ventricular failure is unmasked by the right ventricular assist device. The timing of removal is somewhat variable. As a general guideline, haemodynamic function will either show a recovery within four days or multisystem failure will have supervened; the prognosis is particularly poor when there is apical necrosis.[13]

Management of renal failure in this case was greatly helped by insertion of a haemofilter into the assist device circuit. This allowed removal of water and electrolytes and partial recovery of renal function to a level at which dialysis was no longer required.

This technique may have implications for the long term survival of patients in whom right ventricular failure follows pulmonary embolectomy or closure of postinfarction ventricular defect.

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References

1 Cohn JN, Guiha NH, Broder MI, Limas CJ. Right ventricular infarction. Clinical and hemodynamic features. *Am J Cardiol* 1974;33:209–14.

2 Pennington DG, Merjavy JP, Swatz MT, *et al.* The importance of biventricular failure in patients with postoperative cardiogenic shock. *Ann Thorac Surg* 1985;39:16–25.

3 Myers JL, Parr GVS, Pae WE, Waldhausen JA, Pierce WS. The role of the ventricular assist pump for post-cardiotomy cardiogenic shock: a four and one-half year experience. Proceedings of the third meeting of the ISAO. *Artif Organs* 1981;5(suppl):244–51.

4 Pennington DG, Merjavy JP, Codd JC, Swartz MT, Willman VL. Temporary mechanical support of patients with profound ventricular failure. In: Unger F, ed. *Assisted circulation.* Vol. 2. Berlin: Springer-Verlag: 85–99.

5 Kralios AC, Zwart HHJ, Moulopoulos SD, Collan R, Kwan-Gett CS, Kolff WJ. Intrapulmonary artery balloon pumping. Assistance of the right ventricle. *J Thorac Cardiovasc Surg* 1970;60:215–32.

6 Jett GK, Siwek LG, Picone AL, Applebaum RE, Jones M, Austen WG. Pulmonary artery balloon counterpulsation for right ventricular failure. An experimental evaluation. *J Thorac Cardiovasc Surg* 1983; **86**:364–72.

7 Miller DC, Moreno-Cabral RJ, Stinson EB, Shinn JA, Shumway NE. Pulmonary artery balloon counterpulsation for acute right ventricular failure. *J Thorac Cardiovasc Surg* 1980;**80**:760–3.

8 Gaines WJ, Pierce WS, Prophet GA, Holtzman K. Pulmonary circulatory support. A quantitative comparison of four methods. *J Thorac Cardiovasc Surg* 1984;**88**:958–64.

9 Miyamoto AT, Tanaka S, Matloff JM. Right ventricular function during left heart bypass. *J Thorac Cardiovasc Surg* 1983;**85**:49–53.

10 Pennington DG, Merjavy JP, Codd JE, Swartz MC, Miller LL, Williams GA. Extracorporeal membrane oxygenation for patients with cardiogenic shock. *Circulation* 1984;**70**(suppl I):130–7.

11 Bernhard WF, Schoen FJ, Poirier V, Carr J. A temporary ventricular assist device for patients exhibiting intractable postcardiotomy shock. In: Unger F, ed. *Assisted circulation*. Vol. 2. Berlin: Springer-Verlag: 49–69.

12 Richenbacher WE, Wisman CB, Rosenberg G, Donachy JH, Landis DL, Pierce WS. Ventricular assistance: clinical experience at the Pennsylvania State University. In: Unger F, ed. *Assisted circulation*. Vol. 2. Berlin: Springer-Verlag: 70–84.

13 Bernhard WF, Carr JC, Clay W, *et al*. Clinical and laboratory investigations related to temporary and permanent ventricular bypass. *Heart Transplantation* 1983;3:16–25.

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Chronic proximal aortic dissection presenting as tamponade after 16 years

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SUMMARY A patient presented with tamponade and haemopericardium 16 years after experiencing sudden severe chest pain associated with enlargement of the proximal aorta. Investigations revealed a proximal aortic dissection (DeBakey type II) with extensive laminar and partially calcified thrombus within its false lumen and a large pericardial effusion, which together resulted in a cardiothoracic ratio of 100%. Long term survival after medical treatment of proximal aortic dissection, with such late progression to tamponade, has not been reported before.

The terminal event in more than two thirds of patients who die soon after proximal dissection of the aorta is intrapericardial rupture progressing rapidly to massive haemopericardium and tamponade.[1] Even when it does not cause a haemopericardium, acute proximal aortic dissection carries a poor prognosis.[2] In a review of 425 patients none of those treated medically survived for more than nine years.[1] When patients do survive with chronic aortic dissection, symptoms are most frequently those of congestive heart failure rather than tamponade.

We report a patient in whom tamponade developed 16 years after the initial aortic dissection.

Case report

A 56 year old woman was admitted on 1 October 1985 complaining of breathlessness which had increased progressively over three weeks. She could walk for only 10 yards; she was breathless at rest and dizzy when standing. She also reported epigastric discomfort and anorexia.

She had been treated for hypertension since the age of 27, after having nephritis when she was seven and pyelitis when she was 21. Blood pressure control was poor; in January 1968 it was recorded at 190/130 mm Hg.

In May 1969 when she was 40 she experienced abrupt "excruciating" central chest pain while standing and pulling heavy curtains. This did not radiate and was not pleuritic. It settled after an hour, but later recurred for one more hour. In hospital an initial diagnosis of acute myocardial infarction was not confirmed by any electrocardiographic abnormality nor an increase in cardiac enzymes. One month later persistent chest discomfort and breathlessness developed. Blood pressure was 140/90 mm Hg. Serum haemoglobin was 7·5 g/dl and the erythrocyte sedimentation rate was 100 mm in the first hour. The chest radiograph showed considerable distension of the ascending aorta and arch (fig 1a). A cardiologist suggested that she had a dissection of the aorta but further investigations were not performed.

In 1975 at the age of 46 she reported a two week history of feeling faint and breathless, with sharp chest pains. The chest radiograph (fig 1b) showed an increase in the size of the cardiac silhouette with an abnormal right heart border. Her symptoms were attributed to postural hypotension, and her treatment was changed from methyldopa to oxprenolol. In 1978 she was referred for cardiological investigations because of tiredness, faintness, and palpitation; the cardiothoracic ratio was further increased. Aortography in March 1979 demonstrated a proximal dissection of the aorta (DeBakey type II) with the origin of the false lumen arising a few centimetres above the junction between the right and non-coronary sinuses of Valsalva (fig 2). The cavity of the false lumen was smooth and its neck was well circumscribed; because it was much smaller than the opacity on the chest radiograph the false lumen was thought to contain an extensive

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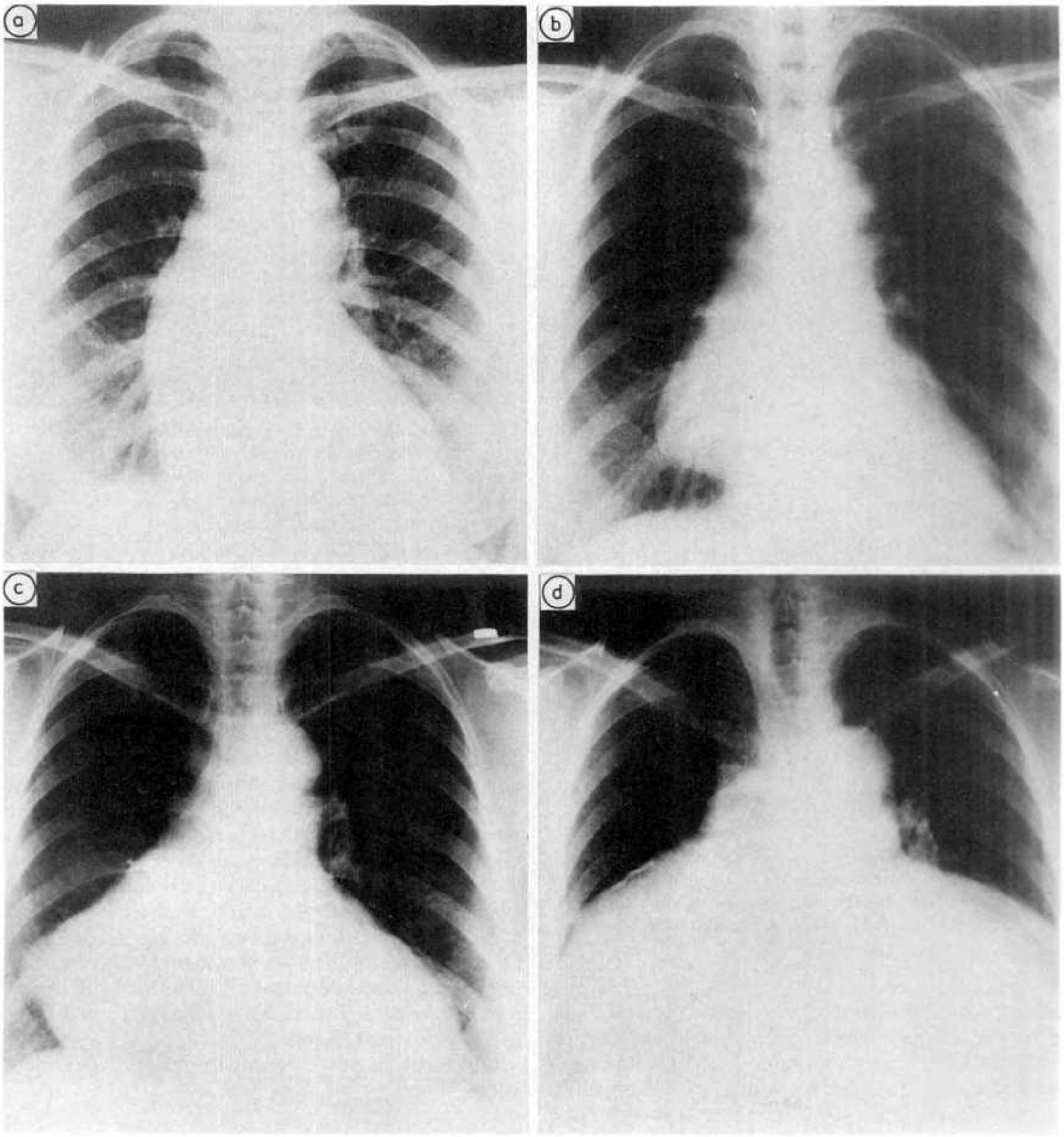

Fig 1 *Serial posteroanterior chest radiographs in a patient with chronic dissection of the proximal aorta. (a) 1969; (b) 1975; (c) 1979, unchanged during follow up to 1982; (d) 1985.*

amount of thrombus. There was no aortic regurgitation. She was referred for elective operation and subsequently admitted, but the operation was postponed because she was symptom free and there had been no change in the radiographic appearances during a 6 month period that she was on the waiting list. She was reviewed as an outpatient until 1982 (see chest radiograph fig 1c) but was then lost to follow up.

On this most recent admission she was unwell, breathless at rest, and centrally cyanosed. She had a sinus tachycardia with poor volume arterial pulses and paradox of 25 mm Hg. The jugular venous pressure was grossly elevated. There was dullness on

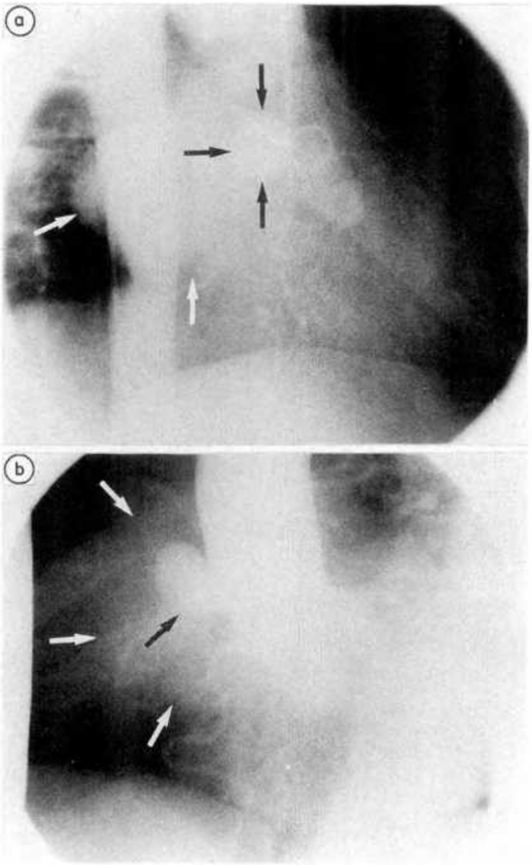

Fig 2 *Right anterior oblique (a) and left anterior oblique (b) projections of the aortogram in 1979, demonstrating the false lumen of a localised proximal aortic dissection (black arrows) with an overlying soft tissue opacity (white arrows).*

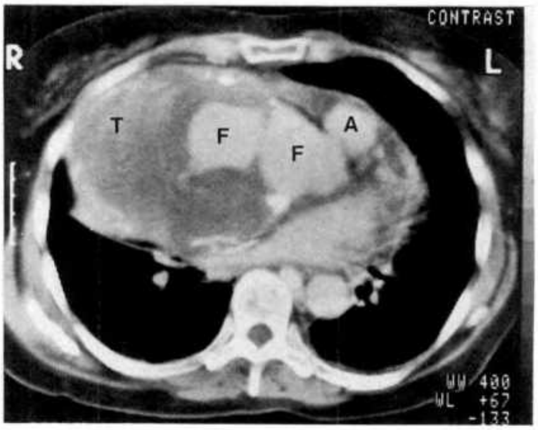

Fig 3 *Computed tomogram at mid-thoracic level after pericardiocentesis, demonstrating contrast enhancement of the ascending thoracic aorta (A) and localised areas of the false lumen of the dissection (F) with overlying thrombus (T) containing peripheral specks of calcification.*

percussion of the precordium and over the right chest anteriorly, with no palpable precordial impulses. The first and second heart sounds were normal and there were no added sounds or murmurs. The electrocardiogram showed low voltage complexes (sum of QRS voltages in limb leads = 8·5 mm), and the chest radiograph showed gross enlargement of the cardiac silhouette (fig 1d). Echocardiography confirmed the presence of a massive pericardial effusion. Two litres of heavily bloodstained fluid with a haemoglobin concentration of 3·7 g/dl were aspirated. Systemic venous haemoglobin concentration was 10·4 g/dl.

Computed tomography with contrast enhancement confirmed the previously documented dissection of the ascending aorta (fig 3). There was a small false lumen and extensive thrombus containing many areas of calcification that enveloped the aorta and extended into the right hemithorax. The transverse and descending thoracic aorta was normal.

Cardiac surgery was performed after instituting femorofemoral bypass. The aortic root was very large; its lateral border expanded outwards and downwards as a saccular dilatation. Incision revealed much organised thrombus within the false lumen of a localised dissection, and after this had been evacuated a 2 cm diameter defect was found in the intima 4 cm above the aortic valve. Histological examination of excised aortic wall demonstrated myxoid degeneration of the media. No single vessel or source was found as a cause of the haemopericardium and tamponade. The intimal defect was repaired with a Teflon felt patch reinforced by a patch of woven Dacron.

She made an uncomplicated recovery from operation.

Discussion

This patient is unusual because she survived for 16 years after a proximal aortic dissection which was treated medically and because she then presented with tamponade.

The circumstantial evidence indicates that she suffered a dissection in 1969, on a background of hypertension and during physical exertion, which is an associated factor in some acute dissections.[3] Thereafter there was a gradual increase in the cardiothoracic ratio, presumably as thrombus continued to be laid down within the false lumen. The episode in 1975 suggests an acute exacerbation of this process, and subsequent treatment with a β adrenoceptor antagonist may have slowed the rate of progression.[4] The most likely cause of the tamponade is that blood gradually leaked into the pericardial cavity from the dissecting haematoma.

About a quarter of patients with aortic dissection present with symptoms that have lasted for more than one month,[3 5] and survival with chronic dissection of the descending or abdominal aorta is well documented. There have, however, been very few reports of dissection of the ascending aorta with survival beyond a few months. Africa *et al* reported a patient who had a dissection for four years.[6] Taber and Lam described a patient with chronic dissection of the descending thoracic aorta (DeBakey type III) who presented with pericardial symptoms after five years.[7] Tamponade has been reported from the late retrograde extension of a type III dissecting aneurysm[8] and from retrograde dissection of an abdominal aortic aneurysm,[9] but we have been unable to find any reports of such late development of tamponade after a chronic type II aortic dissection. In some cases it may be difficult to distinguish between dissection secondary to an atherosclerotic aneurysm and saccular dilatation at the site of a chronic dissection, but in the present case there can be little doubt that the primary event was a localised dissection.

Although thrombus may prevent rupture by acting as a buttress around the aorta,[10] even when proximal dissection is not diagnosed until some weeks after the acute event, operation is indicated because it is usually associated with a good prognosis in these circumstances,[4 11] whereas without operation haemopericardium causes death in 25% of patients.[1] With earlier diagnosis, operation is even more important because tamponade is the fatal event in 80% of patients who have a proximal aortic dissection treated medically.[12]

Dissection of the aorta is the second most common cause of haemopericardium,[13] and chronic dissection should be considered as a cause even when there is no recent history to suggest dissection.

References

1 Hirst AE, Johns VJ, Kime SW. Dissecting aneurysm of the aorta: a review of 505 cases. *Medicine (Baltimore)* 1958;37:217–79.

2 Anagnostopoulos CE, Prabhakar MJS, Kittle CF. Aortic dissections and dissecting aneurysms. *Am J Cardiol* 1972;30:263–73.

3 Slater EE, DeSanctis RW. The clinical recognition of dissecting aortic aneurysm *Am J Med* 1976,60: 625–33.

4 Wheat MW. Acute dissecting aneurysms of the aorta· diagnosis and treatment—1979. *Am Heart J* 1980;99:373–87.

5 Dalen JE, Pape LA, Cohn LH, Koster JK, Collins JJ. Dissection of the aorta: pathogenesis, diagnosis and treatment. *Prog Cardiovasc Dis* 1980;23:237–45.

6 Africa G, Bongiovanni G, Bertoli G. Su di un caso di aneurisma dissecante cronico "guarito" con formazione di "aorta a doppia canna". *Pathologica* 1981;73:105–9.

7 Taber RE, Lam CR. Diagnosis and treatment of chronic dissecting aneurysm of the thoracic aorta *J Thorac Cardiovasc Surg* 1963;45:186–97.

8 Verdant A, Cossette R, Dontigny L, Mercier C, Page A, Page P. Acute dissection of the descending thoracic aorta: repair in an unusual case. *Can J Surg* 1984;27:390–1.

9 Snow N. Hemopericardium from retrograde dissection of an abdominal aortic aneurysm. *Am Surg* 1980;46:589–92.

10 Dinsmore RE, Willerson JT, Buckley MJ. Dissecting aneurysm of the aorta. Aortographic features affecting prognosis. *Radiology* 1972;105:567–72.

11 Miller DC, Stinson EB, Oyer PE, *et al.* Operative treatment of aortic dissection. Experience with 125 patients over a sixteen-year period. *J Thorac Cardiovasc Surg* 1979;78:365–82.

12 Appelbaum A, Karp RB, Kirklin JW. Ascending vs descending aortic dissections. *Ann Surg* 1976;183: 296–300.

13 Barbour BH, Hirst AE, Johns VJ. Nontraumatic hemopericardium. Analysis of 105 cases. *Am J Cardiol* 1961;7·102–8.

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Left atrial metastasis presenting as recurrent embolic strokes

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SUMMARY Tumour emboli from an endocardial metastasis of an endometrial stromal sarcoma caused recurrent and ultimately fatal strokes in a woman of 40. Endocardial metastases are rare. They are known to embolise to the pulmonary and systemic arteries but not to cause recurrent cerebral emboli.

Case report

A 40 year old woman who gave a 3–4 year history suggestive of migraine was admitted with a right hemiparesis and aphasia of sudden onset. She smoked 15 cigarettes per day. She had had unilateral headache usually on the left occurring every few months. On several recent occasions these had been associated with complete loss of vision lasting 20 to 30 minutes. Eighteen months previously a hysterectomy had been performed for menorrhagia. At operation a hard inflammatory mass was found in the sigmoid colon. Histological examination of the uterus revealed stromal adenomyosis which was described as extremely cellular with occasional mitotic figures. A barium enema showed moderate diverticular disease of the sigmoid colon only. Fibreoptic sigmoidoscopy showed no abnormality and the chest radiograph showed a sharply defined circular lesion behind the heart in the left lower lobe of the lung. This was interpreted as a benign cyst.

At admission there was no lymphadenopathy. Blood pressure was 120/80 mm Hg and pulse 80 per minute and regular. No cardiac murmurs or vascular bruits were heard. Examination of the chest and abdomen was normal. There was complete aphasia and a dense right hemiparesis. There was pronounced hyperreflexia on the right with knee and ankle clonus and an extensor right plantar response. After admission she rapidly recovered and 48 hours later had only a mild residual dysphasia.

Initial investigations showed a mild neutrophilia but otherwise normal full blood count and plasma viscosity. Urea, electrolytes, liver function tests, and plasma glucose were normal. Serum cholesterol and triglyceride concentrations were also normal. An electrocardiogram showed only right bundle branch block and no abnormality was seen on the chest radiograph, the previously noted left lower lobe lesion being completely obscured by the cardiac shadow on this occasion. Skull radiographs showed calcification in the falx. Computed axial tomography showed a low density area in the territory of the left middle cerebral artery, indicating an infarct. Treatment with aspirin was started because there appeared to have been a spontaneous arterial occlusion with no obvious precipitating cause.

Four months later she was readmitted with a further episode of transient right hemiparesis and dysphasia. Again there was a rapid recovery. On this occasion the retrocardiac shadow was noted on the chest radiograph and in addition there was a mass at the right hilum. Bronchoscopy was normal. Three weeks later, after a third transient right hemiparesis, she suddenly sustained a dense left hemiparesis associated with loss of consciousness and several grand mal convulsions. There was no improvement in level of consciousness and she died two days later.

A large cystic infarct in the left cerebral hemisphere and a recent haemorrhagic infarct in the right frontoparietal region were found at necropsy. There was a 3·5 cm diameter secondary tumour at the hilum of the right lung and a 2 cm tumour in the left lower lobe. In addition there was a 5 cm diameter tumour in the left atrium (fig 1). There was also a large tumour mass in the pelvis; it involved both ovaries and the rectosigmoid junction. Histological

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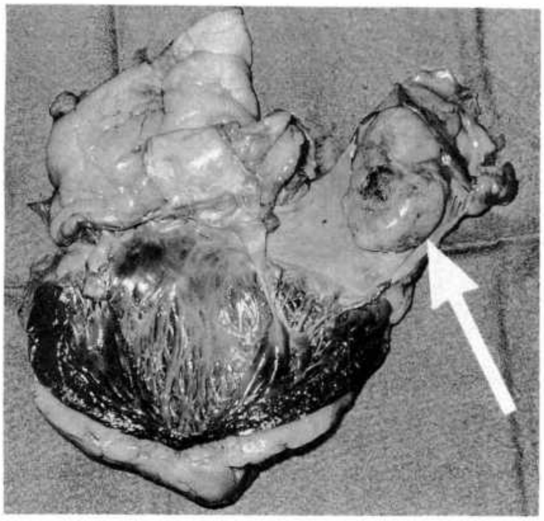

Figure *A 5 cm diameter metastasis arose from the endocardium of the left atrium (arrowed).*

examination showed that these were secondary deposits of an endometrial stromal sarcoma with the same features as the hysterectomy specimen obtained two years before. There was an organised infarct in the spleen but the liver and kidneys were normal. There were atheromatous plaques at the origins of both internal carotoid arteries. A final diagnosis of recurrent cerebral emboli from a left atrial metastasis of an endometrial stromal sarcoma was made.

Discussion

Whereas the myocardium and pericardium are not infrequently the site of metastatic tumours, the endocardium is rarely the site of secondary deposits.[1-3] In 1950 Coller *et al* found only nine cases in published resports.[4] This is presumably because of the rapid blood flow within the heart coupled with the relatively small surface area of the endocardium compared with, say, the vascular bed of the lungs. It may be that endocardial metastases result from tumour cells lodging in subendocardial capillaries, rather than implanting directly on the endocardial surface. In most of the cases in Coller's series the valves were affected, and it has been suggested that valve damage may be a prerequisite for tumour implantation. Thomas *et al* have reported three cases of left atrial metastases, all associated with underlying abnormalities of the mitral valve, of which two had intra-atrial thrombus. They proposed that circulating tumour cells initially lodge in the thrombus.[5] In our case, however, the valves were normal and the atrium contained no thrombus. It is also recognised that an intracardiac secondary tumour can exist within the right atrial cavity as a tumour "culture" without vascular attachment to the endocardium.[6] In the present case the tumour adhered firmly to the endocardium.

Systemic arterial tumour embolism producing effects by vascular occlusion is also rare. It was described in left atrial myxoma[7-9] and as a complication of primary sarcoma of the heart[8] and of left atrial metastases.[5] There are also several reports of systemic embolisation of pulmonary secondaries and primary bronchogenic carcinomas. Embolisation of the latter is liable to occur perioperatively,[10 11] but can be the presenting feature of a bronchogenic neoplasm.[12] Fatal pulmonary embolism of a right atrial metastasis of osteogenic sarcoma has been reported.[6 13] In addition there have been reports of cases of pulmonary metastases directly spreading to the left atrium along a pulmonary vein that were associated with systemic embolisation[14-16] and also a case of recurrent bilateral femoral artery embolism of a metastasis of an osteogenic sarcoma invading the aorta at its bifurcation.[17] Lastly, there is a report of a patient with left ventricular and left atrial endocardial metastases who died of myocardial rupture after tumour embolus to a coronary artery.[18]

The present case had pulmonary as well as intracardiac metastases, so it is conceivable that the pulmonary lesions were the source of the cerebral emboli. There was no evidence of spread along pulmonary veins, however, and we consider it much more likely that the emboli arose from the intracardiac lesion. No tumour emboli were found in the cerebral circulation so we do not know whether the cerebral emboli were fragments of tumour or of an adherent clot. There was no evidence of adherent clot at necropsy and it seems more likely that the small tumour fragments in the cerebral circulation had either dispersed or were simply not visible on the sections examined histologically.

Echocardiography was not performed in this case because a cardiac source of emboli was never suspected from the history and clinical findings. An echocardiographic examination would probably have enabled the diagnosis to be made antemortem; however, this is unlikely to have been of much benefit to the patient. It does, however, emphasise the point that echocardiography is valuable in cases of suspected systemic or cerebral emboli, even in the absence of overt cardiac disease.[19 20]

We believe that recurrent cerebral emboli from an intracardiac metastasis has not been reported before. Intracardiac metastases are rare, but occult cardiac disease can cause transient cerebral ischaemic attacks and echocardiography should be included in the investigation of patients in whom there is no obvious source of emboli.

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References

1 Pritchard RW. Tumors of the heart. Review of the subject and report of 150 cases. *Arch Pathol* 1951;**51**:98–128.
2 DeLoach JF, Haynes JW. Secondary tumors of the heart and pericardium. Review of the subject and report of 137 cases. *Arch Intern Med* 1953;**91**:224–49.
3 Hanfling SM. Metastatic cancer to the heart. Review of the literature and report of 127 cases. *Circulation* 1960;**22**:474–83.
4 Coller FC, Inkey JJ, Moragues V. Neoplastic endocardial implants. Report of a case. *Am J Clin Pathol* 1950;**20**:159–64.
5 Thomas AC, Mills PG, Gibbs NM, Davies MJ. Secondary carcinoma of left atrium simulating myxoma. *Br Heart J* 1980;**44**:541–4.
6 Laurain AR. Intracardial tumor culture of osteogenic sarcoma with fatal tumor embolism. *Am J Clin Pathol* 1957;**27**:664–71.
7 Harvey WP. Clinical aspects of cardiac tumors. *Am J Cardiol* 1968;**21**:328–43.
8 Joynt RJ, Zimmerman G, Khalifeh R. Cerebral emboli from cardiac tumors. *Arch Neurol* 1965;**12**:84–91.
9 Tipton BK, Robertson JT, Robertson JH. Embolism to the central nervous system from cardiac myxoma. Report of two cases. *J Neurosurg* 1977;**47**:937–40.
10 Eason EH. A case of cerebral infarction due to neoplastic embolism. *J Pathol Bacteriol* 1950;**62**:454–7.
11 Prioleau PG, Katzenstein AA. Major peripheral arterial occlusion due to malignant tumor embolism: histologic recognition and surgical management. *Cancer* 1978;**42**:2009–14.
12 Starr DS, Lawrie GM, Morris GC. Unusual presentation of bronchogenic carcinoma: case report and review of the literature. *Cancer* 1981;**47**:398–401.
13 Rastogi DS, Bhalla IP, Chakravorty S. Intracardiac metastasis of osteogenic sarcoma with fatal tumour embolism. (A case report.) *Indian Heart J* 1980;**32**:261–3.
14 Cohen DE, Mora C, Keefe DL. Echocardiographic findings of metastatic chondrosarcoma involving the left atrium. *Am Heart J* 1986;**111**:993–6.
15 Boland TW, Winga ER, Kalfayan B. Chondrosarcoma: a case report with left atrial involvement and systemic embolisation. *J Thorac Cardiovasc Surg* 1977;**74**:268–72.
16 Green WH, Benjamin RS, Ward S, Wiernik PH. Arterial embolism of tumor causing fatal organ infarction. *Arch Intern Med* 1974;**134**:545–8.
17 Van Way CW, Lawler MR. Osteogenic sarcomatous emboli to the femoral arteries. *Am J Surg* 1969;**117**:745–7.
18 Hiraoka K, Ohkawa S, Ueda K, Sugiura M, Shimada H. A case of tumor embolism of the coronary artery, resulting in myocardial infarction and cardiac rupture [Abstract]. *Jpn Heart J* 1976;**17**:269–74.
19 De Bono DP, Warlow CP. Potential sources of emboli in patients with presumed transient cerebral or retinal ischaemia. *Lancet* 1981;i:343–6.
20 Come PC, Riley MF, Bivas NK. Roles of echocardiography and arrhythmia monitoring in patients with suspected systemic embolism. *Ann Neurol* 1983;**13**:527–31.

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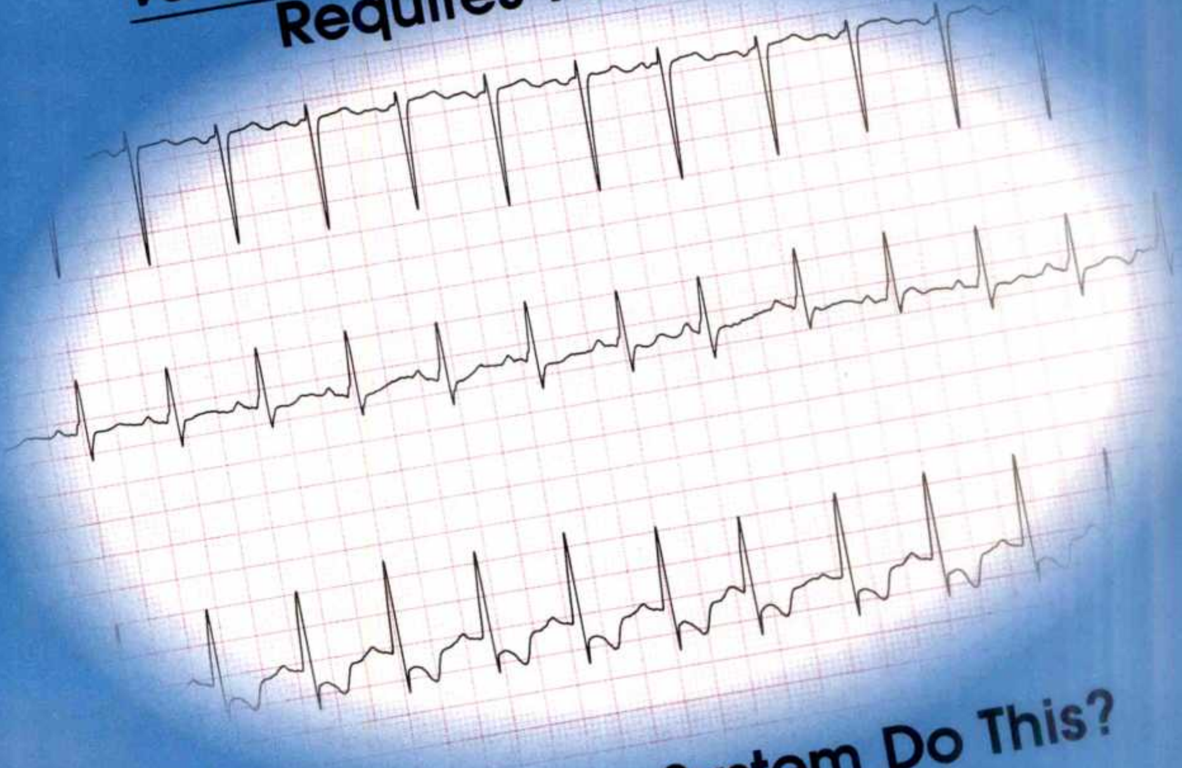

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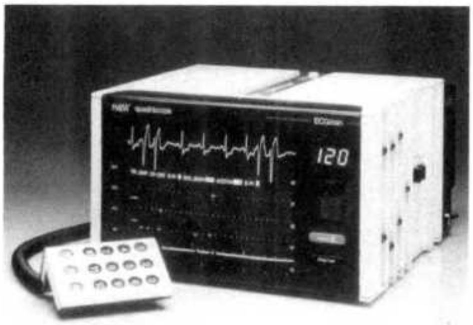

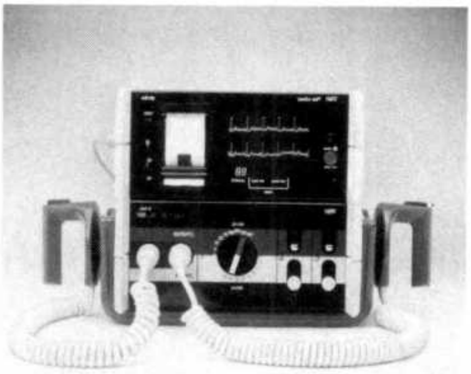

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Anomalous origin of the left coronary artery from the pulmonary trunk: repair after diagnostic cross sectional echocardiography

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SUMMARY An infant with anomalous origin of the left coronary artery from the pulmonary trunk presented with congestive cardiomyopathy. Only cross sectional echocardiography gave a definitive diagnosis. The results of cardiac catheterisation and angiography were inconclusive. Surgical repair was performed successfully after the results of cross sectional echocardiography were known.

There are established guidelines for the diagnosis of anomalous origin of the left coronary artery from the pulmonary trunk by cross sectional echocardiography[1-3] and Doppler echocardiography.[4] But as yet there are no reports of operations on patients in whom the diagnosis of anomalous origin of left coronary artery from the pulmonary trunk was based solely on echocardiography. This is probably because those workers who described the echocardiographic findings also stressed the need for cineaortography as the "definitive investigation in these patients".[1-3] We describe our experience with an infant with anomalous origin of the left coronary artery from the pulmonary trunk who had a repair operation after a cross sectional echocardiographic study clearly showed the defect. The results of cardiac catheterisation were inconclusive. This case has led us to question the need for cardiac catheterisation in some cases of anomalous origin of the left coronary artery from the pulmonary trunk in which a definitive diagnosis can be made by cross sectional echocardiography.

Case report

A two month old infant was referred to our institution for management of congestive cardiomyopathy of recent onset. The history indicated episodes of "turning pale" during feeding. Physical examination showed tachypnoea, tachycardia, weak peripheral pulses, hypotension, an enlarged liver, an enlarged heart, S_3 gallop, and no murmurs. Chest *x* ray showed an enlarged heart with pulmonary oedema. The pattern of the electrocardiogram indicated an anterolateral infarction. The patient improved on digoxin and diuretics. Cross sectional echocardiography clearly showed an anomalous left coronary artery arising from the pulmonary trunk; there was generalised hypokinesia and dilatation of the left ventricle, with paradoxical septal motion and a resultant decrease in the shortening fraction to 15%. The ostium, course, and branches of the left coronary artery were demonstrated to originate from the pulmonary trunk posteriorly and slightly above the cusps of the pulmonary valve (fig a). The right coronary artery was normal. These latter views were obtained from modified high parasternal short axis cuts.[3] Doppler echocardiography showed a normal flow pattern in the pulmonary artery; there was no evidence of late systolic retrograde flow,[4] and moderate mitral regurgitation was detected. A thallium scan showed reduced perfusion in the anterolateral part of the myocardium, which was consistent with the echocardiographic diagnosis.[5]

After these non-invasive tests the patient was examined by cardiac catheterisation and angiography: there was no oxygen saturation step up in the right heart; oxygen saturation was 56% in both the right ventricle and pulmonary artery. Pressure in the pulmonary artery (36/10, $\overline{20}$ mm Hg) was half of systemic pressure while the aortic pressure was 70/45, $\overline{60}$ mm Hg, with normal oxygen saturation of

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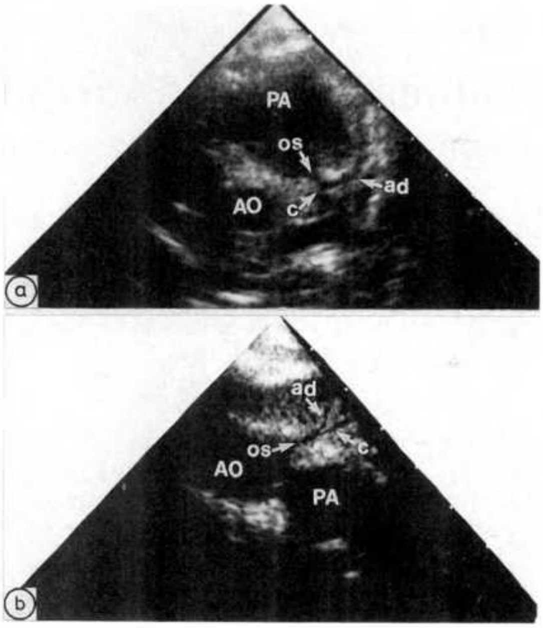

Figure *(a) A modified high parasternal short axis view showing the anomalous origin of the left coronary artery from the pulmonary trunk. (b) Similar view to that shown in (a) from a patient with D transposition of the great arteries showing the origin of the left coronary from the anteriorly located aorta. Notice the similarity of the appearance of the coronary artery originating from the anterior great vessel to the appearance in (a). ad, anterior descending; AO, aorta; c, circumflex; os, ostium of the left coronary artery; PA, pulmonary artery or trunk.*

96%. Aortography failed to demonstrate the origin of the left coronary artery; however, the right coronary artery was well seen and was dominant giving rise to the posterior descending coronary artery. No coronary collaterals were demonstrated. Pulmonary artery injection also did not visualise the left coronary artery.

At operation a median sternotomy was made and the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery was confirmed. A few small collaterals were seen in the vicinity of the anomalous coronary artery; the direction of blood flow in the anomalous coronary artery was difficult to assess. During cardiopulmonary bypass, without aortic occlusion, an end to end anastomosis was created between the left subclavian artery and the left coronary artery. The patient had an uneventful postoperative course and is alive and well 20 months after operation. He continues to take digoxin. His left ventricular shortening fraction remained marginally reduced, until his last visit 20 months ago, when it became normal at 40%. The septal motion has remained dyskinetic with normal posterior wall motion. The left ventricular posterior wall and septal thickness were increased. No residual mitral regurgitation was detected by Doppler echocardiography.

Discussion

In infants the clinical presentation of anomalous origin of the left coronary artery from the pulmonary trunk can resemble that of acute viral myocarditis.[4] In both conditions the electrocardiogram may show an infarction pattern.[5 6] Similarly, the thallium perfusion scan can demonstrate perfusion defects in patients with acute viral myocarditis.[4] Cross sectional echocardiography, however, has been very helpful in differentiating between the two diseases,[2] specifically if the diagnosis of the former is made by direct visualisation of the anomalous origin of the left coronary artery from the pulmonary trunk, rather than by demonstrating the absence of this artery from the aorta.[1]

A dilated right coronary artery is another cross sectional echocardiographic sign of this anomaly. This dilatation is thought to be secondary to the presence of collaterals supplying the left coronary artery from the right.[2 3] In this patient, the presentation was early and probably occurred before the development of collaterals that were large enough to produce a left to right shunt in the pulmonary artery that was detectable either by Doppler echocardiography or cardiac catheterisation. This would also explain the failure of retrograde filling of the left coronary artery and the absence of dilatation of the right coronary artery.[7]

In this case cardiac catheterisation and angiography did not add any information to the diagnosis already made by cross sectional echocardiography and these invasive investigations exposed the infant to additional risks. Some might argue that additional information could be obtained by cardiac catheterisation, for example definition of associated lesions such as anomalous origin of the right coronary artery from the pulmonary trunk.[7] The presence of such an abnormality, however, will not affect surgical management because isolated anomalous origin of the right coronary artery from the pulmonary trunk is benign and usually does not require surgical correction.[7] We propose that after surgical repair and return of ventricular function to normal[8] the risks of cardiac catheterisation will be reduced and other abnormalities will be more easily detected.

Cross sectional echocardiographic examination can give false positive results when it is used to diagnose this anomaly.[1] Nevertheless, we know from our experience of using cross sectional echocardiography to diagnose transposition of the great arteries that when the origin and course of the left coronary artery from the anterior vessel (the aorta) is demonstrated a false positive diagnosis is unlikely. In 10 (91%) of the last eleven consecutive patients with transposition of the great arteries (six males and four females, age 1–90 days), in whom cross sectional echocardiography was used to study the anatomy of the left coronary artery, we were able to demonstrate the origin, course, and proximal branches of the left coronary artery and clearly demonstrate that this originated from the aorta (91%) (fig b). These patients had confirmatory angiographic studies. In anomalous origin of the left coronary artery from the pulmonary trunk in our present patient (fig a and b), and in transposition of the great arteries the left coronary artery originating from the anterior vessels produced similar cross sectional echocardiographic appearances.

This case report indicates that cross sectional echocardiography is a sensitive means of diagnosing an anomalous origin of the left coronary artery from the pulmonary trunk. If this proves to be a consistent finding, the additional risks of cardiac catheterisation and angiography could be avoided in patients with this condition.

We thank Dr S C Chen and Dr I C Balfour for helping us to prepare this paper.

References

1 Robinson PJ, Sullivan ID, Kumpeng V, Anderson RH, Macartney FJ. Anomalous origin of the left coronary artery from the pulmonary trunk: potential for false negative diagnosis with cross sectional echocardiography. *Br Heart J* 1984;**52**:272–7.

2 Caldwell RL, Hurwitz RA, Girod DA, Weyman AE, Feigenbaum H. Two-dimensional echocardiographic differentiation of anomalous left coronary artery from congestive cardiomyopathy. *Am Heart J* 1983; **106**:710–6.

3 Fisher EA, Sepehri B, Lendrum B, Luken J, Levitsky S. Two-dimensional echocardiographic visualization of the left coronary artery in anomalous origin of the left coronary artery from the pulmonary artery: pre and postoperative studies. *Circulation* 1981;**63**: 698–704.

4 King DH, Danford DA, Huhta JC, Gutgesell HP. Noninvasive detection of anomalous origin of the left main coronary artery from the pulmonary trunk by pulsed Doppler echocardiography. *Am J Cardiol* 1985;**55**:608–9.

5 Gutgesell HP, Pinsky WW, DePuey EG. Thallium-201 myocardial perfusion imaging in infants and children: value in distinguishing anomalous left coronary artery from congestive cardiomyopathy. *Circulation* 1980;**61**:596–9.

6 Woods JD, Nimmo MJ, Mackay-Scollay EM. Acute transmural myocardial infarction associated with active coxsackie virus B infection. *Am Heart J* 1975;**89**:283–7.

7 Lurie PR, Takahashi M. Abnormalities and diseases of the coronary vessels. In: Adams FH, Emmanouilides GC, eds. *Moss' heart disease in infants, children, and adolescents*. Baltimore and London: Williams and Wilkins, 1984:501–16.

8 Yoshida Y, Emmanouilides GC, Nelson RJ, Baylen BG, Criley JM. Anomalous origin of the left coronary artery from the pulmonary artery: a case report with remarkable improvement of myocardial function following subclavian artery–coronary artery anastomosis. *Cathet Cardiovasc Diagn* 1980;**6**: 292–303.

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Acquired supravalvar membranous stenosis of the left atrioventricular valve

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SUMMARY Acquired supravalvar membranous stenosis of the left atrioventricular valve developed in a nine year old boy with atrioventricular discordance. The supravalvar membrane had not been present when a partial annuloplasty was performed on the left atrioventricular valve eight years before. The stenosis was relieved by operative excision of the membrane.

Membranous supravalvar mitral stenosis is a well recognised condition of unknown aetiology. Shone *et al* described its association with additional obstructive lesions of the left side of the heart such as parachute mitral valve, subaortic stenosis, and coarctation of the aorta.[1] It may occur, however, as an isolated lesion[2 3] and also in association with the left atrioventricular valve in atrioventricular discordance with ventriculoarterial discordance[4] ("congenitally corrected transposition of the great arteries").

We describe a child with atrioventricular discordance who presented with acquired supravalvar membranous stenosis of the left atrioventricular valve eight years after a partial annuloplasty of the valve ring. Acquired supravalvar stenosis of a prosthetic valve has been described only once before[5] and this present case is the first in which stenosis of the native valve was caused by a thin membrane that was macroscopically similar to the typical membrane of supravalvar mitral stenosis.

Case report

A nine year old boy presented with a four week history of intermittent pyrexia and malaise. On examination he had clinical evidence of stenosis of the left atrioventricular valve and of pulmonary hypertension. There was a prominent parasternal impulse with a long, grade 3/6 apical diastolic murmur and a grade 2/6 apical pansystolic murmur consistent with stenosis of the left atrioventricular valve and mild regurgitation. The pulmonary component of the second sound was accentuated. The respiratory rate was 22 breaths per minute with mild intercostal recession and fine basal inspiratory crepitations.

He was known to have atrioventricular discordance with ventriculoarterial discordance, having presented at three months of age with coarctation of the aorta. Coarctation was repaired by subclavian flap aortoplasty. When he was nine months old a partial annuloplasty was performed on the septal aspect of the left atrioventricular valve because of heart failure caused by atrioventricular valve incompetence. At operation Ebstein's malformation of the left atrioventricular valve was discovered with partial fusion of the septal leaflet and its chordae to the interventricular septum. During follow up there were signs of mild residual valve incompetence and a quiet mid-diastolic murmur thought to represent mild valve stenosis secondary to reduction in the diameter of the valve ring by the annuloplasty.

After the latest admission he continued to have a swinging fever, and bacterial endocarditis was suspected. The electrocardiogram showed complete heart block with a narrow complex escape rhythm at a rate of 70 beats per minute and left atrial hypertrophy. Chest *x* ray showed cardiomegaly with a cardiothoracic ratio of 0 62. There was pulmonary venous distension with diffuse parenchymal lung mottling and interstitial pulmonary oedema.

A cross sectional echocardiogram demonstrated atrioventricular discordance and ventriculoarterial discordance. The left atrium was hugely dilated and there was a normal sized, well functioning systemic ventricle. The left atrioventricular valve appeared thickened with a restricted opening. A supravalve membrane was not suspected; however, later examination of diastolic frames showed a membrane that was separate from the valve (figure). A Doppler ultrasound estimate of flow velocity across the valve showed a peak "e" velocity of 200 cm/s and an end diastolic velocity of 170 cm/s, giving an estimated transvalvar end diastolic gradient of 12 mm Hg. In addition there was mild left atrioventricular valve regurgitation. Catheterisation of the right heart showed a pulmonary artery pressure of 120/50 mm Hg with a mean pressure of 80 mm Hg. The mean pulmonary artery wedge pressure was 20 mm Hg. The left heart was not catheterised because bacterial endocarditis was suspected. A pulmonary arteriogram and follow through showed a dilated left atrium with a stenosed immobile left atrioventricular valve.

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Extensive investigations did not find a cause for the pyrexial illness. His cardiac failure became worse, with increasing renal impairment, and so replacement of the left atrioventricular valve was recommended. At operation a thin membrane was found that originated from the atrial aspect of the left atrioventricular valve and was closely apposed to the valve cusps. The membrane was attached to the left atrium near the site of the previous partial annuloplasty and was circular with a small central orifice. The macroscopic appearance was identical to that of "typical" membranous supravalvar mitral stenosis. The membrane was excised and the valve ring was mobilised. Afterwards the valve appeared to be competent with a satisfactory valve orifice diameter. Left atrial pressure after repair was 12 mm Hg with a systemic pressure of 85/65 mm Hg and a pulmonary artery pressure of 60/35 mm Hg.

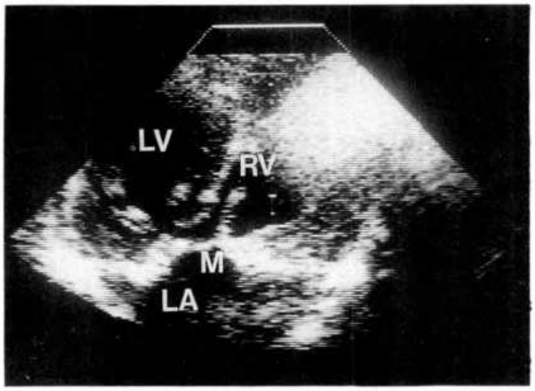

Figure *Modified apical cross sectional echocardiogram (diastolic frame) showing the supravalvar membrane (M) closely apposed to the left atrioventricular valve. LA, left atrium; RV, right ventricle; LV, left ventricle.*

Postoperative echocardiographic assessment showed a mobile left atrioventricular valve with Ebstein's malformation as previously noted. Doppler assessment showed successful relief of the stenosis with a peak "e" velocity of 180 cm/s and no evidence of an end diastolic gradient. There was mild valve regurgitation.

Four weeks after operation the swinging pyrexia recurred and chest *x* ray examination showed an increase in the diffuse pulmonary shadowing that had been attributed to pulmonary venous hypertension before operation. Open lung biopsy showed severe pulmonary vascular hypertensive disease with features that indicated a superimposed arteritic process. Treatment with steroids was started and he has remained well and apyrexial during six months of follow up.

Discussion

Supravalvar membranous stenosis of the mitral valve is a potentially curable condition that even with very careful echocardiographic assessment may be difficult to differentiate preoperatively from mitral valve stenosis.[6] If mitral valve stenosis is erroneously suspected, surgical correction of supravalvar stenosis in younger children may be delayed because valve replacement is usually deferred until an adequate sized prosthetic valve can be inserted. In our patient supravalvar stenosis was not considered because the membrane was not present when valve annuloplasty was performed eight years before.

The aetiology of the membrane is uncertain. It is possible that it resulted from an inflammatory reaction to the suture material used for the previous annuloplasty; however, suture material was only present on the septal aspect of the valve and the membrane was circular with a central orifice. Alternatively, it is possible that the annuloplasty resulted in a fold of redundant tissue in the left atrium that progressively encroached upon the valve because of the mechanical forces exerted upon it by the slightly narrowed valve orifice. The isolated occurrence of supravalvar membranous stenosis of the mitral valve, however, indicates that this cannot be the explanation in all cases. It is unlikely that there is a direct link between the pyrexial illness and the development of the supravalvar membrane because there were signs of important stenosis of the left atrioventricular valve for several years before the development of the pyrexial illness that was attributed to a vasculitis.

Acquired supravalvar mitral stenosis has been described once previously. The obstruction was caused by a dense fibrous tissue reaction at the insertion site of a prosthetic valve.[5] The obstructing tissue had a different macroscopic appearance from the membrane described in our case in which the membrane was thin and pliable.

This case illustrates the difficulty of diagnosing this rare condition before operation and raises questions about the aetiology of supravalvar membranes. If operation has been performed on the atrioventricular valve the possibility of an acquired supravalvar membrane should be considered when signs of atrioventricular valve stenosis subsequently appear.

We are grateful to Professor M H Yacoub for his assistance and advice about this patient.

References

1 Shone JD, Sellers RD, Anderson RC, Adams P, Lillehei CW, Edwards JE. The developmental complex of "parachute mitral valve", supravalvar ring of left atrium, subaortic stenosis, and coarctation of aorta. *Am J Cardiol* 1963;11:714–25.

2 Chung KJ, Manning JA, Lipchik EO, Gramiak R, Mahoney EB. Isolated supravalvar stenosing ring of left atrium: diagnosis before operation and successful surgical treatment. *Chest* 1974;64:25–8.

3 Otero Coto L, Martin Judez V, Juffe A, *et al*. Supravalvular stenotic mitral ring. A new case with surgical correction. *J Thorac Cardiovasc Surg* 1976;71:537–9.

4 Chesler E, Beck W, Barnard CN, Schrire V. Supravalvar stenosing ring of the left atrium associated with corrected transposition of the great vessels. *Am J Cardiol* 1973;31:84–8.

5 Rogers AK, Morgan JR, Forker AD, Fosburg RG. Supravalvular stenosis after disc mitral valve replacement. *J Thorac Cardiovasc Surg* 1971;62:810–2.

6 Sullivan ID, Robinson PJ, de Leval MR, Graham TP. Membranous supravalvar mitral stenosis: a treatable form of congenital heart disease. *J Am Coll Cardiol* 1986;8:159–64.

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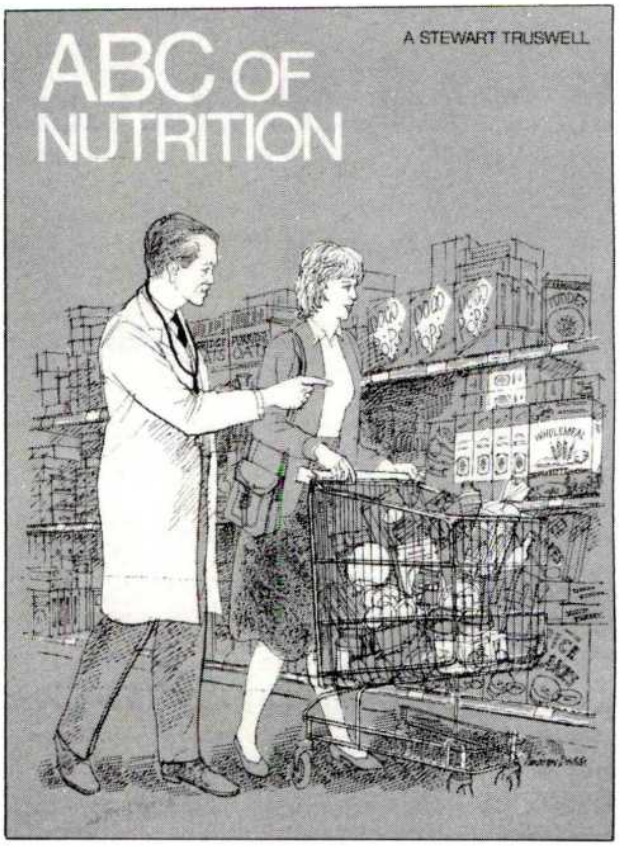

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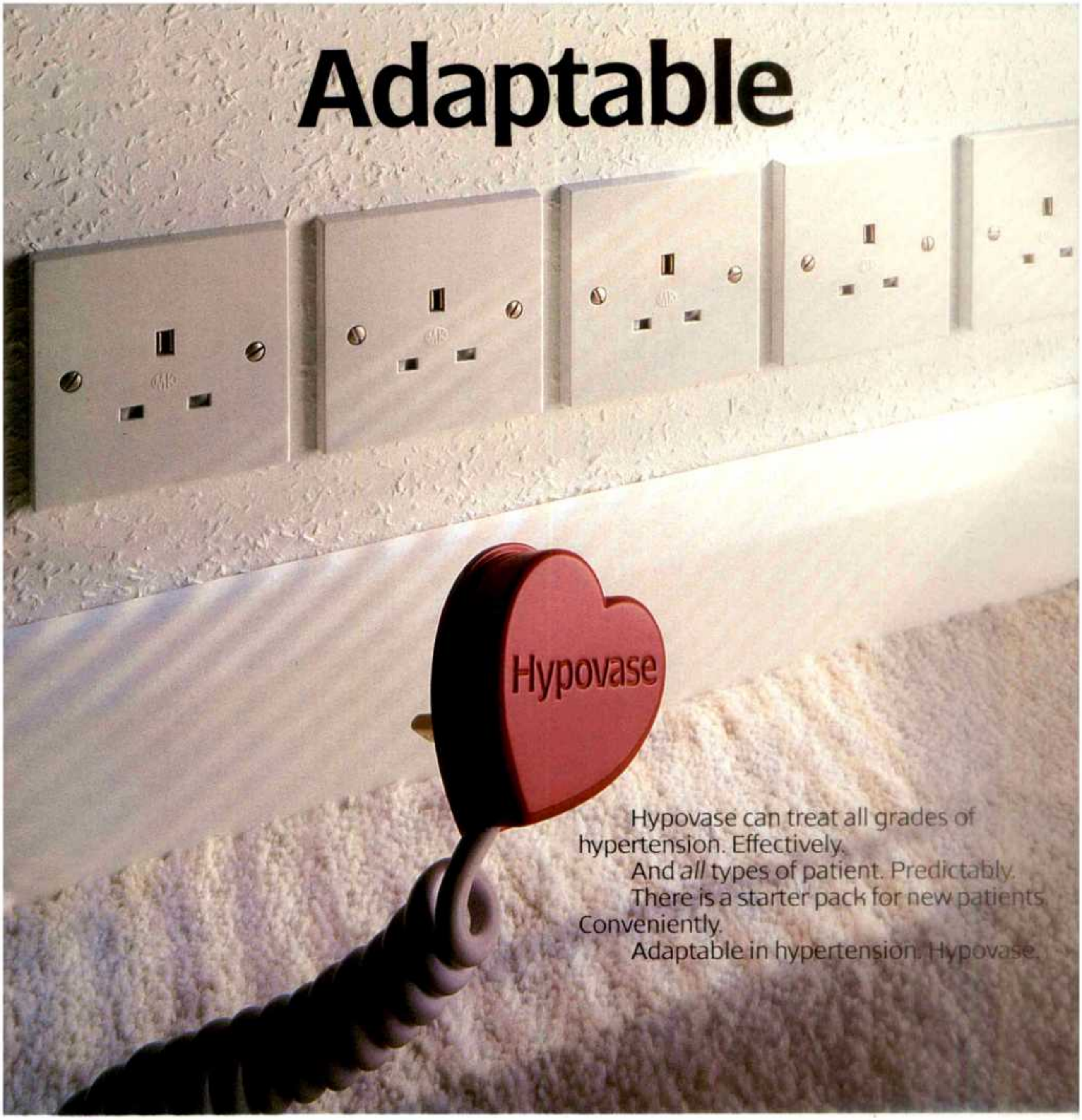

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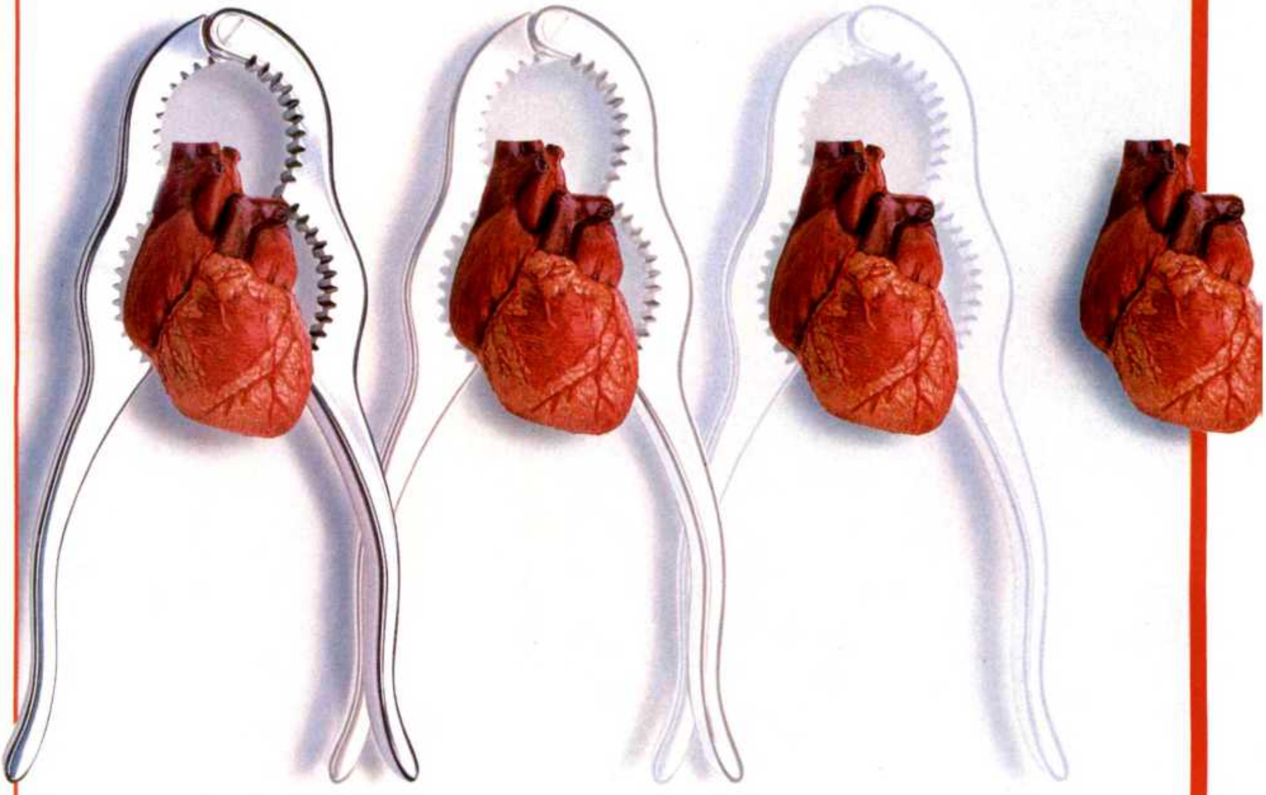

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Adalat® 10 mg nifedipine capsules for angina Adalat 5® 5 mg nifedipine capsules for angina in the elderly. Prescribing Information. Presentation: Adalat/Adalat 5: Orange soft gelatin capsules containing a yellow viscous liquid. Adalat capsules overprinted with 'ADALAT' and the Bayer Cross contain 10 mg nifedipine. Adalat 5 capsules overprinted with 'ADALAT 5' and the Bayer Cross contain 5 mg nifedipine. **Indications:** For the treatment and prophylaxis of angina pectoris, and for the treatment of Raynaud's phenomenon. **Dosage and Administration:** For oral administration, the capsules should be taken with a little fluid during or after meals. The recommended dose is one 10 mg capsule three times daily. If necessary, up to two 10 mg capsules three times daily may be taken. If an immediate effect is required, the capsule should be bitten open and the liquid contents allowed to remain in the mouth. Adalat 5 capsules permit titration of initial dosage in the elderly and those patients on concomitant medication. The recommended dose is one Adalat 5 capsule three times daily. For the treatment of Raynaud's phenomenon the recommended dose is one 10 mg capsule three times a day with subsequent titration of dose according to response, to a maximum of two 10 mg capsules three times a day. **Contra-indications, warnings, etc. Contra-indications:** Must not be given to women capable of child bearing. **Warnings and Precautions:** Adalat is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8-10 days. Adalat may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adalat will not prevent possible rebound effects after cessation of antihypertensive therapy. Adalat should be used with caution in patients whose cardiac reserve is poor. Ischaemic pain has been reported in some patients, commonly within 30 minutes of the introduction of Adalat therapy. Patients experiencing this effect should discontinue Adalat. The use of Adalat in diabetic patients may require adjustment of their control. The anti-hypertensive effect of nifedipine can be potentiated by simultaneous administration with cimetidine. When used in combination with nifedipine, serum quinidine levels have been shown to be suppressed regardless of dosage of quinidine. **Side Effects:** Adalat is well tolerated. Minor side effects, usually associated with vasodilatation are mainly headache, flushing, and lethargy. These effects are transient and invariably disappear with continued treatment. Gravitational oedema associated with increased capillary filtration capacity has been reported. There are reports of gingival hyperplasia which may regress on withdrawal of therapy. Rare cases of hypersensitivity-type jaundice have been reported. **Overdosage:** Standard measures such as atropine and noradrenaline may be used for resultant bradycardia and hypotension. Intravenous calcium gluconate may be of benefit combined with metaraminol. **Pharmaceutical Precautions:** The capsules should be protected from strong light and must be stored in the manufacturer's original container. **Legal Category:** POM. **Pack Quantities:** Adalat and Adalat 5 capsules are available in foil strips of 10 in packs of 100. **Daily Treatment Cost:** Adalat: 37p per 3 capsules. Adalat 5: 25p per 3 capsules. **Product Licence Numbers:** Adalat: PL 0010/0021. Adalat 5: PL 0010/0079.

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Jubilee Editorial

Hypertension

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Over the past 40 years hypertension has been a special focus of interest for research workers in Britain. Great contributions have been made by researchers in other lands but this editorial must be forgiven a mildly parochial outlook because it is part of a series written to celebrate the Golden Jubilee of the British Cardiac Society. In a wide field of investigation there are four areas in which the contribution of the United Kingdom was particularly notable. The first of these was the description of the pathological features of severe hypertension.

Pathology

In a sense it all began when, long before the first measurements of blood pressure in man, Richard Bright observed that patients dying of nephrosclerosis often had enlarged hearts.[1] But the meticulous pathological observations of Volhard and Fahr in Germany[2] marked the beginning of the modern vascular pathology. Fahr's description of "partial infarction" of the kidney has never been surpassed. The only real flaw was an excessive emphasis upon vasospasm as a cause of the abnormality. Serious work on experimental hypertension came only after Goldblatt's discovery of the renal artery clip in the 1930s.[3] His methods were taken up by Clifford Wilson and Frank Byrom at the London Hospital, who used them in several important experiments on the time course and reversibility of hypertension produced by the renal artery clip.[4]

The visual impact of later studies by Byrom of the pial arteries of the hypertensive rat, observed through an implanted transparent skull window, was stunning.[5] I can still remember the impression they made on me at a Medical Research Society demonstration at the start of my own research career. At about the same time Kincaid-Smith, McMichael, and Murphy[6] completed an extensive correlative study of the clinical and pathological features of a large series of patients with accelerated hypertension seen at Hammersmith just before the dawn of the modern era of treatment.

Because of their accessibility the fundus oculi have always had a special place in research on hypertensive vascular disease. Many physicians assume that it all began with Keith, Wagener, and Barker's famous paper from the Mayo Clinic in 1939, in which they correlated retinal features with prognosis.[7] In fact they were far from the first to describe the features or identify the prognosis. As early as 1859, Liebreich, in Germany, had described linear streaks of blood, milk white spots, a reddish papilla, engorged veins, and abnormal retinal arteries in patients with Bright's disease.[8] In 1886 Bull in the United States followed up 86 patients with neuroretinitis and found that 57 died within a year.[9] Notable descriptions of the more subtle arterial and venous changes in the hypertensive fundus were made by the British ophthalmologists Marcus Gunn (1898) and Foster Moore (1916).[10 11] But Keith, Wagnener, and Barker had the blood pressure readings as well as the clinical description, and their paper deserves its reputation.

The Glasgow ophthalmologist Robert Leishman established the clinicopathological correlation of the fundal changes in hypertension.[12] The coming of fundus photography, and particularly fluorescein angiography, made it possible to follow the evolution of areas of fibrinoid necrosis in retinal arteries in man and experimental animals, which showed up as areas of fluorescein leakage. From these studies the pathogenesis of the cotton wool spot was deduced.[13 14] It was my singular good fortune to participate in that exciting era of retinal research with Paul Henkind and Norman Ashton from the Institute of Ophthalmology.

Epidemiology

The second great contribution of the British in-

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vestigators was to the epidemiology of hypertension. The family studies carried out by Pickering, Hamilton, Fraser Roberts, and Sowry and St Mary's were highly original in their conception. No doubt history is right to give George Pickering most of the credit for conceiving this study but the contribution of the statistician Fraser Roberts goes largely unrecognised. Yet it was probably his skill that converted a good piece of clinical research into a classic study.[15] Later this work became one of the centrepieces of the famous Platt-Pickering controversy that enlivened the columns of the *Lancet* in 1963.[16]

A different view of the genetics of hypertension had emerged in Robert Platt's department in Manchester. Vivid arguments about the relative merits of camels with two humps and dromedaries with one echoed up and down the land. By general agreement Pickering won the argument by demonstrating that the bimodal distribution of blood pressure in Platt's data was an artefact of digit preference and avoidance. One consequence was a much more exact approach to clinical blood pressure measurements in which Geoffrey Rose was a leader[17] notably with his ultimate weapon against digit preference—the London School of Hygiene and Tropical Medicine sphygmomanometer.

It is fascinating to speculate that Platt's ghost may ride again when the molecular biologists crack the hypertension genes. Hypertension demonstrates polygenic inheritance and the risk is graded with the pressure. But the number of important genes will probably turn out to be small and it would not be surprising to find that the cardiovascular risks conveyed by each of them are different. Who would be judged the victor then? Perhaps both Platt and Pickering—we shall see.

Prospective studies of defined populations have played a very important part in understanding the risks of mild increases in blood pressure. The early studies by Miall[18] in the mining valleys of South Wales were of a high standard, but later the palm crossed the Atlantic and all the really important prospective studies, such as Framingham, Albany, Tecumseh, were done in the United States.[19] Why didn't the United Kingdom play a bigger part? Perhaps the gulf that existed between many clinicians and epidemiologists at the time was unbridgeable.

Pathogenesis

The study of pathogenesis is the third area in which there have been substantial contributions from the United Kingdom. Stanley Peart took leave from St Mary's to work with Elliott at the National Institute for Medical Research and together they elucidated the peptide sequence of angiotensin.[20] Nowadays sequencing a short peptide is a simple matter but then it was a tour de force. Peart's work on the renin-angiotensin system was continued at St Mary's, and later at Glasgow, by the troika of Brown, Lever, and Robertson. Perhaps their greatest contribution was to take apart the assay of renin so that it became an accurate measurement of renin content, calibrated against a defined biological standard. Much of our knowledge of the role of renin in conditions like renal artery stenosis and Addison's disease came from that era.[21] John Dickinson, while still at University College Hospital, used his electronics know-how and mechanical ingenuity to devise a system for giving prolonged subpressor infusions of angiotensin to rabbits.[22] The progressive increase in the pressor effect which he observed is one of the few positive feedback loops known in biology. Currently, attention in the renin angiotensin field has shifted to renin in the vessel wall and several groups in the United Kingdom are actively engaged.[23]

Modern interest in the role of sodium retention on the regulation of blood pressure can be traced back to Borst's experimental work with liquorice in Holland. Borst was not a charismatic figure and received little credit in his own country or elsewhere but his observations were important and original.[24] Work on sodium retention received a tremendous boost when the Taits, working at the Middlesex Hospital Medical School, using the novel paper chromatographic methods for steroid separation that had been devised by Ian Bush, identified a new salt retaining steroid in the adrenal gland and called it "electrocortin".[25]A short time later electrocortin became aldosterone. Considering the importance of the discovery, they must have come close to winning the Nobel prize, but Jim Tait and Ian Bush received only modest recognition in their own land. The names we tend to remember are those of the Americans Arthur Guyton and Jerome Conn rather than those of Borst, Bush, and Tait. Both Guyton, who constructed computer models of the haemodynamic and renal interactions that led to an increase in blood pressure, and Conn, who discovered primary hyperaldosteronism, made great independent contributions; but we had our own heroes. Jack Ledingham at the London devised ingenious methods for measuring cardiac output in conscious rats so that the changes that took place as the blood pressure rose after a renal clip could be studied.[26]

These experiments did much to establish Guyton's model. Cuthbert Cope at Hammersmith, who made many contributions to the study of the steroids, was only days behind Conn in hunting for electrocortin excess in a patient with "potassium losing renal disease".[27]

Drug treatment

The fourth component of hypertension research in the United Kingdom has been the study of drug treatment of hypertension. As it is the part of the story which I know best I hope that I may be forgiven for devoting greater attention to it.

Early clinical memories are always the most powerful. My first memory of severe hypertension is as a very junior clinical student in the early 1950s. I was clerking a patient admitted to an ear, nose, and throat ward with an epistaxis who was found to have a very high blood pressure and papilloedema. After the bleeding stopped she was discharged on the grounds that the condition was untreatable. I was shocked because during my intercalated BSc in physiology, a few months before, I had read papers about pentolinium tartrate. Three years later as a house officer with Melville Arnott in Birmingham I had first hand experience of how difficult it was to manage patients with malignant hypertension with pentolinium and mecamylamine. At that time some patients with the most refractory hypertension had bilateral adrenalectomy and under replacement with cortisone. The aim was to find a precarious ledge between death from addisionian crisis on the one hand and malignant hypertension on the other. It was a challenging experience for a preregistration house officer. If the blood pressure was brought under control there was dramatic clinical improvement. Pulmonary oedema vanished like magic, deterioration of renal function halted, and retinal cotton wool spots and papilloedema quickly regressed.

I leap forward 29 years to a press conference at the Medical Research Council in July 1986 at which members of the MRC Hypertension Trial Working Party, chaired by Peart, were trying to explain to a distinctly unimpressed group of journalists how they had screened half a million people, treated 18 000 of them with very mild hypertension for five years, and had prevented 60 strokes and 5 myocardial infarcts and saved 12 lives.[28] So much had happened in between.

The dawn broke with the synthesis of a series of polymethylene quaternary ammonium compounds. This was followed by precise pharmacological studies by Paton and Zaimis at the Royal College of Surgeons.[29] The clinical initiative was seized by Smirk in Dunedin.[30] He had been a Professor of Pharmacology in Cairo (as had Gaddum before him) before becoming a Professor of Medicine so had a prepared mind and a proper sense of the priorities. His abstract in the *New Zealand Medical Journal* in 1950 describing the reversal of the clinical features of malignant hypertension represents the beginning of the modern era of antihypertensive treatment. His findings were quickly confirmed by McMichael at Hammersmith and Rosenheim at University College Hospital. May and Baker, the British subsidiary of the French company Rhone Poulenc had an important role in developing the quaternary ammonium compounds for clinical use.

There followed a period of explosive discovery of active compounds in the pharmaceutical industry and ever widening indications for their use. Mecamylamine (Merck, United States) and pempidine (May & Baker, Dagenham) overcame the problems of poor bioavailability and tolerance that hampered the use of the quaternary ammonium ganglion blocking drugs.[31 32] Bretylium tosylate (Burroughs Wellcome, Beckenham) was the first selective inhibitor of adrenergic neurones and spared patients from the miserable parasympathetic side effects of ganglion blockade.[33] I have a memory of leaving a meeting about bretylium in conversation with Max Rosenheim around 1960. To him bretylium represented the ultimate that was likely to be achieved in selective sympathetic blockade. Nearly three decades and several generations of more selective drugs later this seems hard to believe. Despite its high initial promise bretylium, like pentolinium a quaternary ammonium compound, was felled by the rapid development of tolerance. Fortunately, guanethidine discovered by the Ciba company in the United States was close behind.[34] The same company had earlier developed hydralazine but this drug was not much used in Britain at the time. The late Franz Gross, who played a leading role in the development of hydralazine,[35] was wont to say that British doctors nearly destroyed the drug by giving excessive doses and causing a great deal of avoidable toxicity. Reserpine was another important drug discovery from a medicinal plant long known in India. Its properties were drawn to the attention of the Western world by an article by Vakil in the *British Heart Journal*.[36] Use of high doses and suicides among several patients in Britain and New Zealand blackened the name of this drug but it is still widely used on the mainland of Europe.

The real revolution began with the discovery of chlorothiazide by Karl Beyer and his colleagues at Merck, Sharp & Dohme in the United States.[37] Chlorothiazide and its many congeners were well tolerated, easy to regulate, and potentiated the action of most other antihypertensive drugs. They opened the door to an era of mass treatment. Methyldopa, whose blood pressure lowering action was discovered by Oates and Sjoerdsma at the National Institutes of Health,[38] was also developed by Merck, Sharp & Dohme. These two drugs played a central part in the ever widening use of antihypertensive drugs during the decade between 1960 and 1970. It was also a time that saw clinical pharmacology beginning to come into its own because of the need to study the new powerful drugs in a more systematic way than the clinical anecdotes and testimonials of the past.

Meanwhile the search for more specific drugs went on and after some encouraging indications from other workers the team under James Black at Imperial Chemical Industries produced pronethalol and later propranolol.[39] Angina was the main clinical target; it was during a carefully conducted angina trial that Prichard observed a small but systematic reduction in blood pressure.[40] His persistence in studying the hypotensive effect of beta blockade in comparison with other powerful established drugs (and in the face of some opposition) finally led to the wide recognition that propranolol was an essential therapeutic agent. Through its introduction hydralazine and other vasodilators gained a second lease of life. Propranolol began to replace reserpine in the "combos" beloved on the Continent and the "stepped-care" of North America.

The calcium antagonists verapamil and nifedipine from Knoll and Bayer in Germany[41] also came into antihypertensive treatment by way of the treatment of angina. By contrast, the angiotensin converting enzyme inhibitors were discovered by the Squibb company in the United States as a result of a deliberate search after the orginal observations of biological activity in snake venom.[42]

Throughout this period the United Kingdom maintained a good reputation for accurate and critical studies of new antihypertensive drugs. To do so at a time when enormous commercial forces were unleashed was no small contribution. Two factors seem to have helped. The first was the expertise of the specialist hypertension clinics that had been founded in a number of major hospitals (Hammersmith, University College Hospital, Oxford, Manchester, Sheffield, Chelmsford) to handle the ganglion blocking drugs. The existence of the National Health Service made long term specialist follow up easier than it was in the private fee-based systems in other countries.

Another positive influence was the rise of clinical pharmacology as a clinical and laboratory discipline. Possibly it was not in the long term interest of clinical pharmacology that so many of the founding fathers of the subject in the United Kingdom adopted hypertension as their disease but it did mean that considerable expertise was deployed. Antihypertensives, especially the β blockers, became the model for exact studies of pharmacodynamics and kinetics in man. With the oculomucocutaneous syndrome with practolol, diabetes with diuretics, haemolytic anaemia with methyldopa, systemic lupus with hydralazine, and nephrotic syndrome with captopril it also became the training ground for clinical toxicologists.

In the first decade of modern treatment, when almost all the patients had very high pressures, there was convincing clinical evidence of benefit. Retinal haemorrhages, cotton wool spots, and papilloedema resolved[43] and pulmonary oedema melted away. In the second decade, most patients still had pretreatment diastolic pressures above 110 mm Hg. On treatment their heart often got smaller, electrocardiographic evidence of left ventricular hypertrophy regressed,[44] symptoms such as morning headaches disappeared,[45] and deaths from cerebral haemorrhage or rapidly progressive renal failure became rare.[46] In the third decade (from about 1970 onwards) the nature of the problem changed. Many patients had diastolic pressures of only 100 mm Hg or lower and few had any signs or symptoms related to hypertension. The aim of treatment was to prevent cerebral and coronary vascular disease and clinical assessment was of little help. This was the stage when the large trials of outcome came into their own.

It would be wrong to end this account of a glorious period of discovery and innovation in drug treatment like the end of a Hollywood movie with the heroes walking off into the sunset. Only a few of the new drugs were developed from the outset as antihypertensives. Most of the others arose from intelligent pursuit of chance observation in animals or man. Some of the most spectacular examples of drug toxicity have arisen with antihypertensives. Much of the toxicity was (and is) dose related and therefore potentially avoidable. Often the first descriptions of toxicity came from the United Kingdom. Some reports were the result of excessive enthusiasm for high doses but often alert long term follow up led to the early recognition of toxicity and some estimate of incidence. The British record on outcome trials has been patchy. Hamilton carried out a promising but very small trial in Britain,[47] but it was Freis in the United States who initiated the only substantial placebo controlled trials of treatment of moderate and severe essential hypertension during the period that treatment was being rapidly extended.[48] By the early 1970s the issue was becoming pressing because millions of patients with mild hypertension were being considered for treatment. In 1971 the Medical Research Council agreed to conduct a trial in mild essential hypertension. I had some part in the decision, having written to the Secretary of the Medical Research Council to suggest a trial; the Medical Research Council received similar advice from its epidemiology committee at about the same time. Bill Miall, and later Gillian Greenberg with the collaboration of many general practitioners performed the vast work of recruiting patients and guiding the trial to a successful conclusion. And so it was that 14 years later we met at the Medical Research Council head office under the chairmanship of W S Peart to tell the press what we had discovered. It did not seem much: a 45% reduction in stroke (the trial numbers had been calculated on the basis of a 40% reduction); a powerful adverse effect of cigarette smoking; and no more than a hint of benefit for myocardial infarction in one subgroup. But my overriding impression of the 36 years since Smirk is not that we put too much effort into outcome trials but that we put far too little. The prospect for the next 10–15 years is not encouraging with many new drugs and little new outcome data (the trial pipeline is almost empty). It is not the best legacy to have left our successors.

References

1 Bright R. Tabular view of the morbid appearances in 100 cases connected with albuminous urine. With observations. *Guy's Hosp Rep* 1836;1:380–402.
2 Volhard F, Fahr T. *Die Brightsche Nierenkrankheit. Klinik, Pathologie und Atlas*. Berlin: Springer, 1914.
3 Goldblatt H, Lynch J, Hanzal RF, Summerville WW. Studies on experimental hypertension I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med* 1934; 59:347–79.
4 Wilson C, Byrom FB. The vicious circle in chronic Bright's disease. Experimental evidence from the hypertensive rat. *Q J Med* 1941;**10**:65–94.
5 Byrom FB. The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension. Experimental evidence from the hypertensive rat. *Lancet* 1954;**ii**:201–11.
6 Kincaid-Smith P, McMichael J, Murphy EA. The clinical course and pathology of hypertension with papilloedema (malignant hypertension). *Q J Med* 1958; 27:117–53.
7 Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their cause and prognosis. *Am J Med Sci* 1939;**197**:332–43.
8 Liebreich R. Ophthalmoskopischer Befund bei Morbus Brightii. *Albrecht Graefes Arch Ophthalmol* 1859;5:265–8.
9 Bull CS. Analysis of 103 cases of exudatice neuroretinitis, associated with chronic Bright's disease. *Trans Am Ophthalmol Soc* 1886;4:184–94.
10 Gunn M. On ophthalmoscopic evidence of general arterial disease. *Trans Ophthalmol Soc UK* 1898;**18**: 356–81.
11 Moore RF. Retinitis of arteriosclerosis and its relation to renal retinitis and to cerebral vascular disease. *Q J Med* 1916;**10**:29–77.
12 Leishman R. The eye in general vascular disease: hypertension and arteriosclerosis. *Br J Ophthalmol* 1957;**41**:641–701.
13 Dollery CT, Henkind P, Ramalho PS, Paterson JW, Hill DW. Focal retinal ischaemia. Part 2. Ultrastructural changes in focal retinal ischaemia. *Br J Ophthalmol* 1966;**50**:285–324.
14 Garner A, Ashton N, Tripathi R, Kohner EM, Bulpitt CJ, Dollery, CT. Pathogenesis of hypertensive retinopathy: an experimental study in the monkey. *Br J Ophthalmol* 1975;**59**:3–44.
15 Hamilton M, Pickering GW, Roberts JAF, Sowry GSC. The aetiology of essential hypertension. 4. The role of inheritance. *Clin Sci* 1954;**13**:273–304.
16 Platt R. Heredity in hypertension. *Lancet* 1963;**i**: 899–904.
17 Rose GA, Holland WW, Crowley EA. A sphygmomanometer for epidemiologists. *Lancet* 1964;**i**; 296–300.
18 Miall WE. Follow-up study of arterial pressure in the population of a Welsh mining valley. *Br Med J* 1959;**ii**:1204–10.
19 The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events. Final report of the Pooling Project. *J Chronic Dis* 1978;**31**:201–306.
20 Elliott DW, Peart WS. The amino acid sequence in a hypertensin. *Biochem J* 1957;**65**:246–54.
21 Brown JJ, Davies DL, Lever AF, Robertson JIS. Variations in plasma renin concentration in several physiological and pathological states. *Can Med Assoc J* 1964;**90**:201–6.
22 Dickinson CJ, Lawrence JR. A slowly developing pressor response to small concentrations of angiotensin: its bearing on the pathogenesis of chronic renal hypertension. *Lancet* 1963;**i**:1354–6.
23 Swales JD. Arterial wall and plasma renin in hypertension. *Clin Sci* 1979;**56**:293–8.
24 Borst JGG, Borst-de Geus A. Hypertension explained by Starling's theory of circulatory homeostasis. *Lancet* 1963;**ii**:677–82.
25 Simpson SA, Tait JF, Bush IE. Secretion of a salt retaining hormone by the mammalian adrenal cortex. *Lancet* 1952;**ii**:126–8.
26 Ledingham JM, Cohen RD. Circulatory changes during reversal of experimental hypertension. *Clin Sci* 1962;**22**:69–77.
27 Cope CL, Harwood M, Pearson J. Aldosterone secretion in hypertensive diseases. *Br Med J* 1962;**i**: 659–73.
28 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J* 1985;**291**:97–104.
29 Paton WDM, Zaimis EJ. The pharmacological actions of polymethylene bis-trimethylammonium salts. *Br J Pharmacol* 1949;4:381–400.
30 Restall PA, Smirk FH. The treatment of high blood pressure with hexamethonium oxide. *NZ Med J* 1950;**49**:206–9.
31 Stone CA, Torchiana ML, O'Neill GQ, Beyer KH. Ganglionic blocking properties of 3-methylaminoisocamphane hydrochloride (mecamylamine), a secondary amine [Abstract]. *J Pharmacol Exp Ther* 1956;**116**:54–5.
32 Spinks A, Young EHP. Polyalkylpiperidines: a new series of ganglion blocking agents. *Nature* 1958;**181**: 1397–8.
33 Boura ALA, Copp FC, Duncombe WG, Green AF,

McCoubrey A. The selective accumulation of bretylium in sympathetic ganglia and their post-ganglionic nerves. *Br J Pharmacol* 1960;**15**:265–70.

34 Maxwell RA, Plummer AJ, Schneider F, Povalski H, Daniel AI. Pharmacology of [2-(Octahydro-1-Azocinyl)-ethyl]-guanidine (SU-5684). *J Pharmacol Exp Ther* 1960;**128**:22–9.

35 Gross F, Druey J, Meier R. Eine neue Gruppe blutdrucksenkender Substanzen von besonderem Wirkungscharakter. *Experientia* 1950;**6**:19–21.

36 Vakil RJ. Clinical trial of Rauwolfia Serpentina in essential hypertension. *Br Heart J* 1949;**11**:350–5.

37 Beyer KH. The mechanism of action of chlorothiazide. *Ann NY Acad Sci* 1958;**71**:363–79.

38 Oates JA Jr, Gillespie L Jr, Crout JR, Sjoerdsma A. J. Inhibition of aromatic amino acid decarboxylation in man and associated pharmacological effects. [Abstract]. *J Clin Invest* 1960;**39**:1015.

39 Black JW, Duncan AM, Shanks RG. Comparison of some properties of pronethalol and propranolol. *Br J Pharmacol* 1965;**25**:577–91.

40 Prichard BNC. Hypotensive action of pronethalol. *Br Med J* 1964;**i**:1227–8.

41 Fleckenstein A. Specific inhibitors and promoters of calcium action in the excitation-contraction coupling of heart muscle. In: Harris P, Opie L, eds. *Calcium and the heart*. London: Academic Press, 1971.

42 Ondetti MA, Rubin B, Cushman DW. Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. *Science* 1977;**196**:441–4.

43 Hodge JV, Dollery CT. Retinal soft exudates. A clinical study by colour and fluorescence photography. *Q J Med* 1964;**33**:117–31.

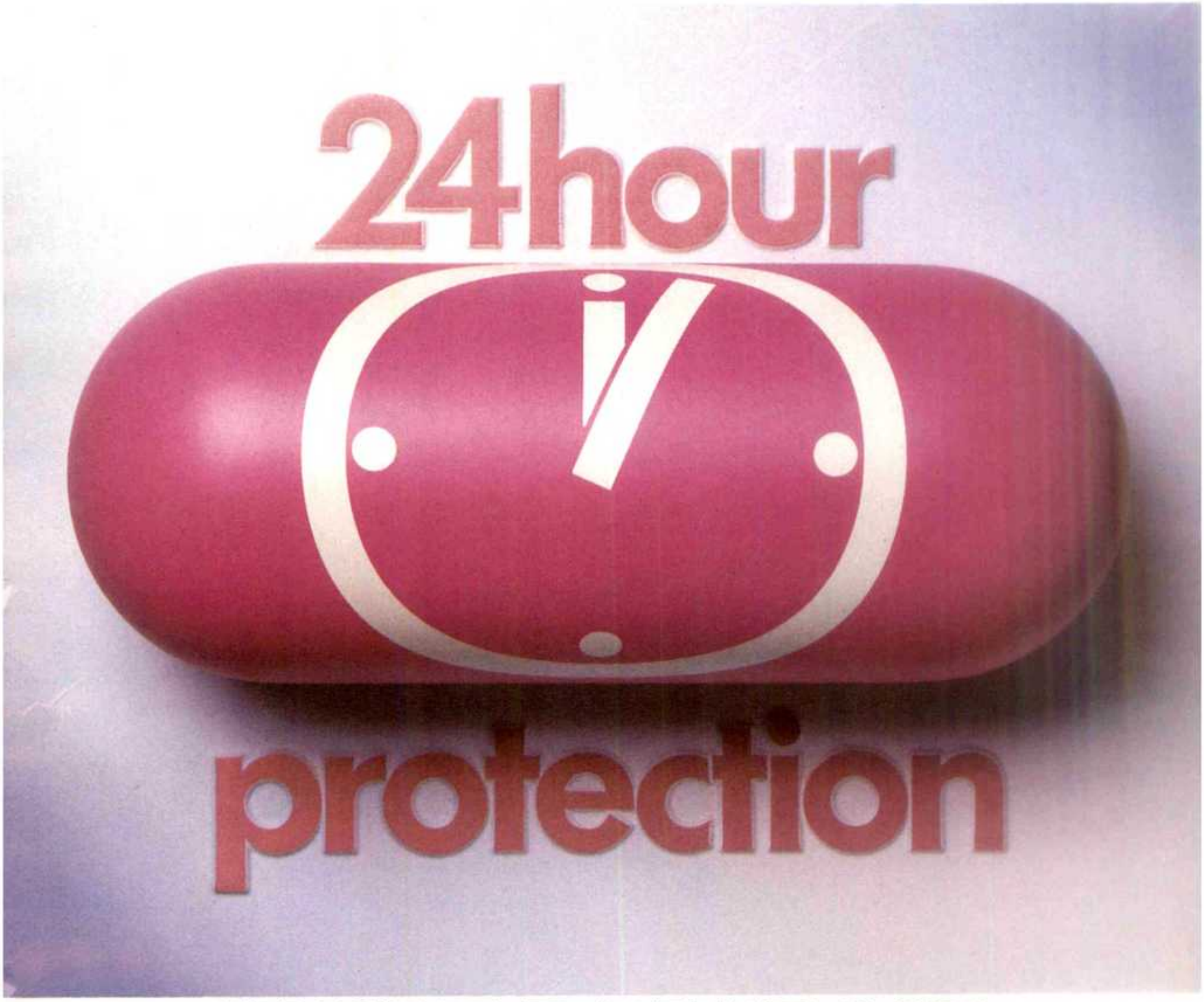
44 George CF, Breckenridge AM, Dollery CT. Value of routine electrocardiography in hypertensive patients. *Br Heart J* 1972;**34**:618–22.

45 Bulpitt CJ, Dollery CT, Carne S. Changes in symptoms of hypertensive patients after referral to hospital clinic. *Br Heart J* 1976;**38**:121–8.

46 Breckenridge A, Dollery CT, Parry EHO. Prognosis of treated hypertension—changes in life expectancy and causes of death between 1952 and 1967. *Q J Med* 1970;**39**:411–29.

47 Hamilton M, Thompson EN, Wisniewski TKM. The role of blood pressure control in preventing complications of hypertension. *Lancet* 1964;**i**:235–8.

48 Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic pressures averaging 115 through 129 mm Hg. *JAMA* 1967;**202**:1028–34.



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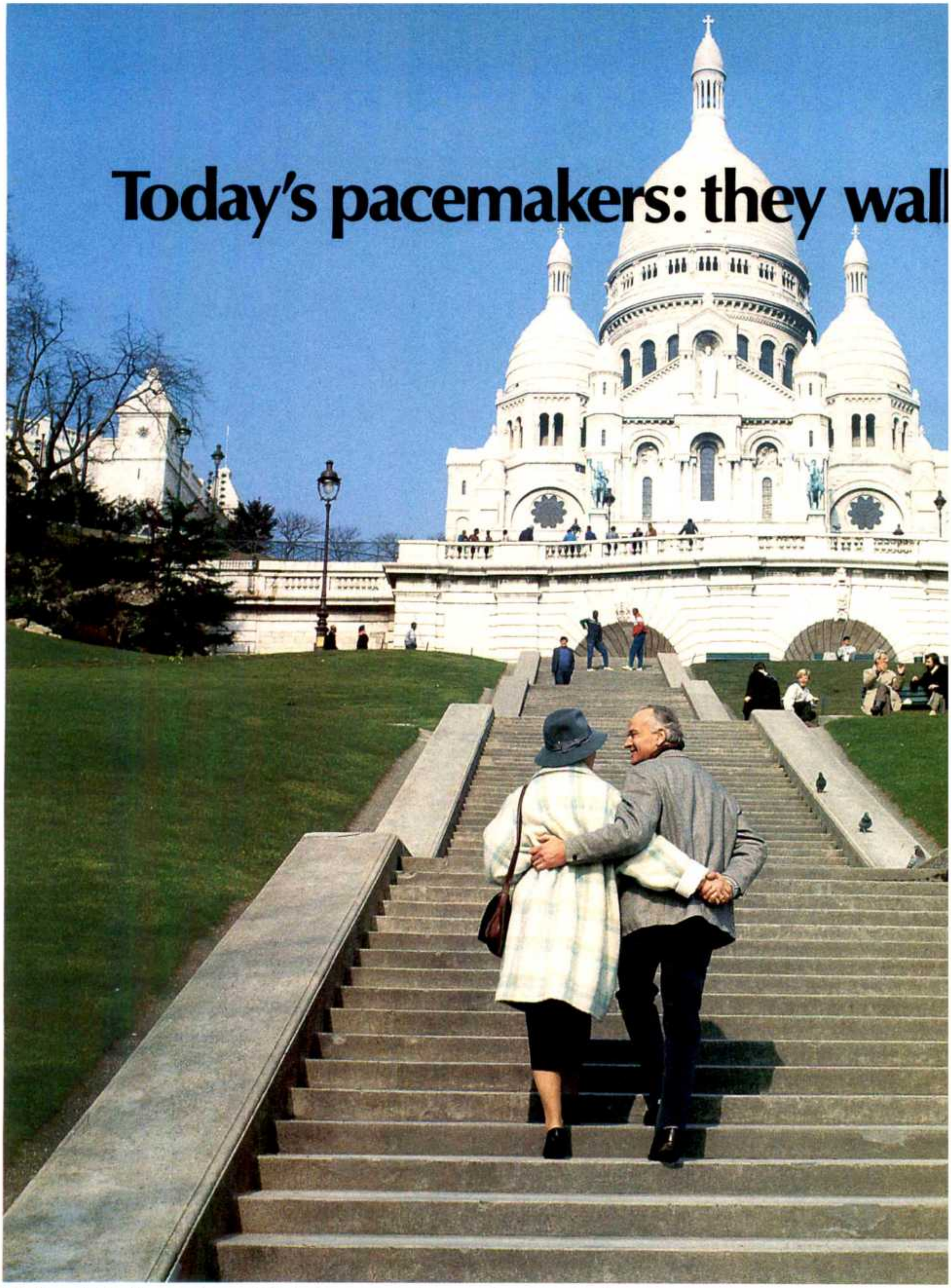

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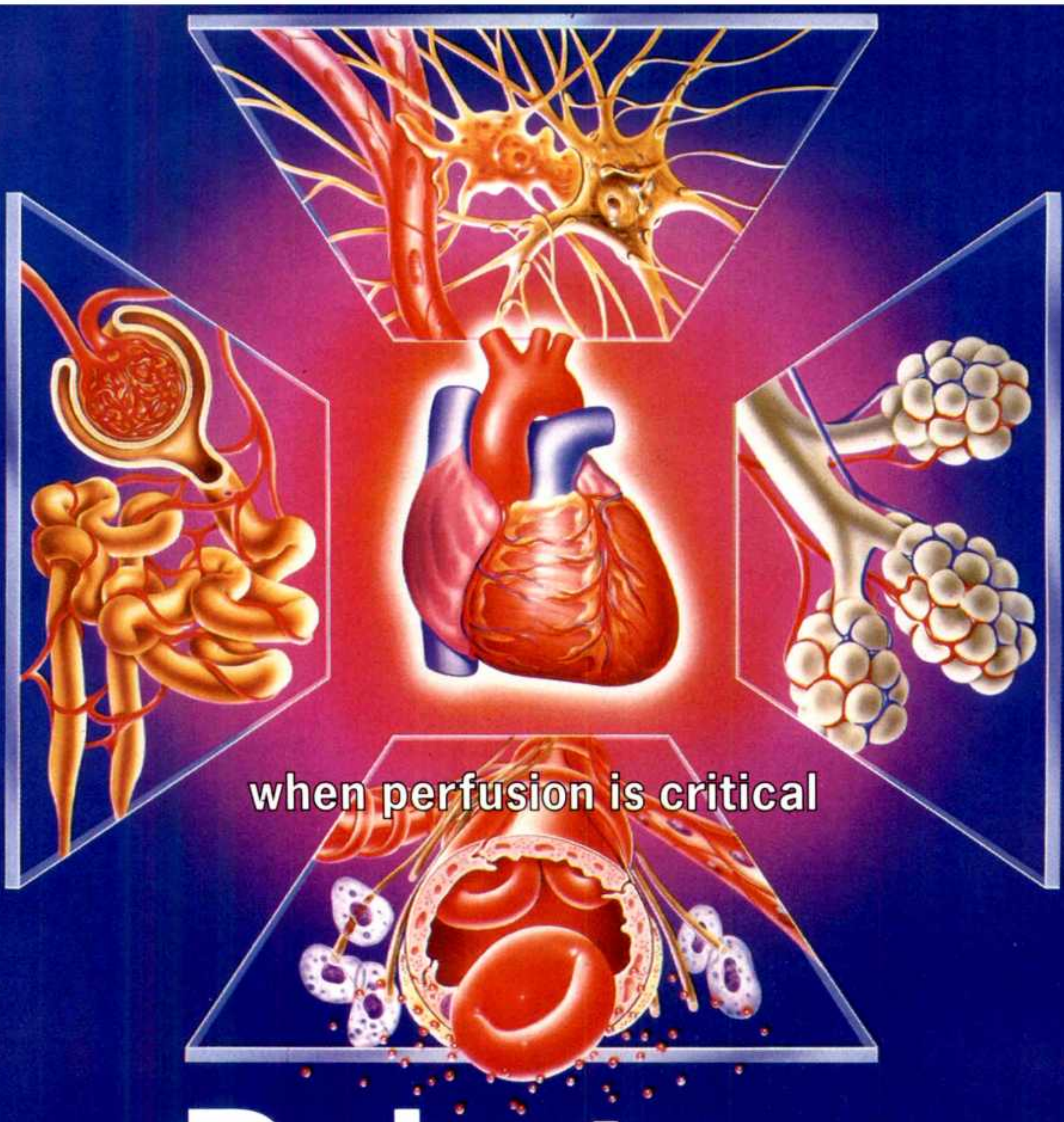

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Br Heart J 1987;58:185–9

Editorial

Assessing the success of percutaneous transluminal coronary angioplasty

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The goals

Evaluation of the success of a therapeutic procedure should be related to the technical and clinical goals set for that procedure. For percutaneous transluminal coronary angioplasty the goal set depends on the clinical circumstances. For stable angina pectoris it is the elimination of exertional ischaemia; however in an elderly patient or a patient with severe associated non-cardiac disease, in whom coronary artery bypass surgery would be too hazardous, the goal may be limited to reducing the severity of angina pectoris to acceptable levels. There may also be a secondary goal of reducing the risk of subsequent major cardiac events, such as acute myocardial infarctions or improving prognosis. The intention in unstable angina is also to eliminate ischaemia but in some cases prevention of an impending infarction and conversion of the symptoms from an unstable pattern to a stable pattern may be an acceptable therapeutic result. During an evolving acute myocardial infarction caused by coronary occlusion angioplasty may be used to open the artery and reduce the stenosis sufficiently to limit the extent of the myocardial infarction and preserve left ventricular function. Here it may not be advisable or desirable to attempt to dilate the artery to the extent that might be attempted in a patient with stable angina pectoris and single vessel disease. Similarly, when there is chronic total occlusion of a vessel, angioplasty can be used to achieve dilatation sufficient to permit anterograde flow in that artery before attempting dilatation of another artery. If the second artery becomes occluded at angioplasty, flow in collaterals from the first artery may avoid catastrophic haemodynamic collapse.

Measuring success

An inherent criterion of success in all these situations is not to harm the patient. So procedures causing death or myocardial infarction or requiring emergency coronary artery bypass grafting because of acute occlusion or dissection are by definition unsuccessful. Apart from these major complications and the inability to cross and dilate the lesion at all, there are few cases in which an operator will view the procedure as "unsuccessful". Procedures which do not improve the degree of stenosis (perhaps because there is dissection) but where occlusion is not total and bypass is not required may belong to this category. Such patients would generally be considered for coronary bypass surgery, which is the normal, though not the exclusive, alternative treatment for angina pectoris in patients in whom angioplasty is attempted.

Whenever specific numerical angiographic criteria are used to define success, there is a reasonable natural tendency to classify as successful any procedure in which the above criteria for lack of success are not met. It may therefore be more realistic to define as successful, procedures that are not clearly failures, although there will be a subgroup of these "successful" procedures that could more accurately be classified as "partially successful". Perhaps the most relevant question is "did we do what we came to do?"

Primary success

Most published reports refer to the "primary success" of angioplasty rather than its "clinical success". Primary success is based on angiographic criteria and the technical goal is to reduce the angiographic stenosis to an acceptable level. This will vary with the clinical situation and the coronary anatomy. Unfortunately, such variability is difficult to handle statistically and investigators found it is more con-

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venient to use standard criteria. An early definition of primary success used in the landmark paper by Gruentzig and coworkers when they described the results in their first 32 patients was a 10% reduction in diameter stenosis or gradient.[1] Since angiographers generally use diameter stenosis rather than area stenosis in referring to numerical degrees of stenosis this convention will be followed here. Subsequently Gruentzig and coworkers regarded a reduction in angiographic stenosis of $\geqslant 20\%$ as indicative of primary success,[2] although they also used reduction in stenosis to 50% or less as the main criterion for successful angioplasty,[3] and this latter definition has also been used by other workers.[4] The registry of the National Heart, Lung, and Blood Institute adopted the criterion of 20% reduction in stenosis,[5] and other workers have followed this guideline.[6 7] Other definitions of primary success have, however, been reported, including a decrease in stenosis by 40% or greater,[8 9] residual stenosis $\leqslant 40\%$,[10] and at least a 35% reduction in the initial percentage stenosis with post-angioplasty stenosis of 50% or less.[11]

One difficulty with the 20% reduction definition advocated by Gruentzig and coworkers is that the patient may be left with a residual stenosis of 70–80% and still be classified as a success. Sometimes this may be valid but in many patients residual exertional ischaemia would be expected, or recurrent symptoms associated with "restenosis" may be more likely. On the other hand, using criteria such as a residual stenosis of $<40\%$ strictly would result in lower primary success rates and in a significant number of patients the procedure may erroneously be classified as unsuccessful, since in a patient with "subtotal" obstruction (so-called "99%" or "98%" stenosis) and unstable angina, reduction of the stenosis to 60% may result in a definite clinical success. The term "partial success" may be used to describe such a patient but this term has not really been used to any extent in published reports, presumably because mixtures of degrees of success are more difficult to handle statistically.

The term "partial success" may also relate to patients with multivessel disease in whom success may be achieved in one or more vessels but not in all. In these patients the term success refers to procedural success for the individual patient rather than to technical success of dilatation of an individual lesion. For example, in a patient with occlusion in one vessel and 90% stenosis in another, an attempt at reopening the occluded vessel may be unsuccessful whereas the dilatation of the stenosed vessel may be successful both angiographically and clinically, since in many cases treatment of the "culprit" or "target" lesion can result in clinical success without the need for "complete" revascularisation.[12]

Part of the problem of defining primary angiographic success is the inaccuracy inherent in the angiographic measurement of percentage diameter stenosis. This can be particularly difficult when there is intimal dissection. There is considerable interobserver and intraobserver variability in these measurements,[13] and unless they are made blind by an independent observer, with or without computer assisted analysis, it is all too easy for any sort of angiographic improvement to be fitted to the given criteria for angiographic primary success. Even computer assisted calliper based techniques for analysis of data before and after angioplasty can be biased. Completely automated computer analysis systems may minimise this bias but these are not always practical for individual lesions. Such systems are reported to give lower estimates of stenosis than visual interpretation alone.[14 15] These difficulties make the precise definitions of angiographic success less useful and perhaps less valid than they might initially appear.

Although in some cases medical treatment may be considered the primary alternative, in most cases the true alternative is coronary artery bypass surgery. It may therefore be helpful to consider the success of angioplasty in the same terms as coronary artery bypass surgery. Defining primary success by a loose angiographic criterion such as any "angiographic improvement" or reduction in stenosis not associated with one of the major complications[16] is rather like defining coronary artery bypass surgery as initially successful if the patient gets out of the operating room alive with bypass grafts in place. In a sense this is valid and many reports on coronary artery bypass surgery have focused on mortality rates. A similar loose and "unscientific" definition of primary success for angioplasty is often used in practice if not in print; and bearing in mind the difficulties inherent in the strict numerical angiographic definitions and the considerable variation in these definitions the less scientific interpretation may perhaps be more useful. Ideally, the definition of primary success should relate to the clinical circumstances and therefore to the goal in an individual patient. At one extreme, primary angiographic success in the setting of acute myocardial infarction may be simply defined as angiographic patency with prompt opacification of the distal vessel,[17] whereas for stable angina pectoris with single vessel disease a residual angiographic stenosis of $\leqslant 50\%$ may be regarded as a success because this would be expected to eliminate the symptoms. In many cases a less than ideal result could be regarded as a partial success.

Measurement of gradients across the lesions at the time of the procedure have also been used to evaluate the success of percutaneous transluminal coronary angioplasty. If the gradient is reduced to <15 mm Hg there is a better chance of long term success without the need for repeat angioplasty,[18] and some workers have included a gradient criterion in their definition of primary success, that is a reduction to 15 mm Hg[11] or 10 mm Hg.[4] This type of criterion is difficult to use clinically because there are technical difficulties with measurement with the balloon in position and with some balloon systems it is not possible to measure translesional gradient. In an individual patient it is hard to know what a high residual gradient means in terms of clinical success and in many cases attempting to reduce the gradient to a low level may be detrimental. This means that judgement and angiographic appearance have to be used in each case before proceeding to use a larger balloon, higher pressures, or longer inflation times. If a residual gradient of <15 mm Hg is used as a criterion for success[11] a considerable number of patients with a higher residual gradient may still end up with a technically and clinically successful angioplasty. Certainly, restricting the term "success" to patients with a residual gradient of <10 mm Hg[4] will unreasonably exclude many adequate procedures as primary successes. Coronary flow reserve has been used in a limited number of institutions to assess the results of angioplasty and to relate this to gradients,[19] but this is really a research procedure and is unlikely to be clinically useful. It requires complex computer digital analysis which is not generally available.

Clinical success

"Secondary" or "clinical" success may be more important to the patient than primary angiographic success. Most patients who undergo coronary angioplasty have symptoms of angina or of acute myocardial ischaemia. Elimination of these symptoms, or at least a reduction to an acceptable level consistent with the patient's desired life style, would be a reasonable definition of clinical success. In some patients who manifest "silent ischaemia", however, the procedure may be undertaken primarily because of a positive stress test in the absence of clinically significant symptoms. Nevertheless, most of these patients will have had some symptoms or a cardiac event, such as subendocardial infarction, to warrant stress testing in the first place. Defining clinical success as a decrease in one anginal class[11] may not be very realistic because a patient with class IV unstable angina may end up with class III angina on minor exertion and be classified as a success; and for most patients this would not be a reasonable improvement. This may, however, be considered a partial success, or even a complete success if the goal of the procedure were to "buy time" by stabilising a patient with multivessel disease before elective coronary bypass surgery. Nevertheless, standards for judging percutaneous transluminal coronary angioplasty should be as strict as those for bypass surgery. Decrease in anginal symptoms to grade II or less should be the minimum standard for success of angioplasty in most patients. If the criteria for clinical success are less strict than those for primary success the clinical success rate may be higher than the primary success rate,[11] implying that primary "failures" become clinical successes. A primary "failure" should theoretically make a patient a candidate for alternative treatment, usually bypass surgery, but such a referral would not be appropriate if the primary "failure" is associated with clinical success.

Problems with the subjective definition of clinical success by classification of symptoms make objective evidence of myocardial ischaemia resulting from a coronary artery stenosis an important part of the assessment of the patient before and after percutaneous transluminal coronary angioplasty. Many patients have objective non-invasive stress studies before angioplasty that confirm the presence of myocardial ischaemia associated with symptoms of angina. In these patients a repeat stress test after the procedure showing negative results or an improvement to within acceptable levels would indicate clinical success. Several studies have shown improvement in stress tests with or without radionuclide multiple gated acquisition or thallium studies.[14 20] In some patients with unstable angina or pre-infarction angina, relief of the unstable symptoms may be all that is required to establish clinical success, if this is the primary clinical goal of undertaking the procedure. In many of these cases an exercise test is not undertaken before the procedure because the symptoms are unstable. A subsequent positive exercise test with symptoms of stable exertional angina may still be consistent with the clinical success of the initial procedure, even if a second procedure is necessary to achieve further dilatation of the vessel or to dilate other vessels in a patient with multivessel disease. The optimal timing of such a post-angioplasty stress test has not been established. If it is too early the patient may not be able to exercise adequately because of groin discomfort. If it is done very late we may be seeing the effects of restenosis rather than those of inadequate initial dilatation. It is possible that some of the "restenosis" that is identified from positive stress tests after angioplasty is in fact inadequate initial dilatation. On the other hand, very early testing may not take into account possible "remoulding" of an artery after angioplasty, especially when there has been intimal dissection. Pacing stress tests immediately after angioplasty have been used to assess the effects of the procedure on coronary flow[21] and we have used pacing combined with echocardiography or digital ventriculography in a few selected cases to document a functional improvement immediately after angioplasty. The value of such an early stress test in predicting subsequent progress remains to be determined and this type of test is unlikely to be widely applied. An exercise test performed at 2–3 weeks would avoid most of the difficulties.

When "primary" success is defined by angiographic criteria, "secondary" clinical success may be defined by symptomatic criteria which tend to be subjective, or by functional physiological criteria that take into account objective evidence of myocardial ischaemia, or by a combination of symptomatic and physiological criteria. The more objective assessment is particularly important in patients with "silent ischaemia" and in patients with "atypical" chest pain in whom some of the symptoms may not be cardiac in origin. If such objective functional criteria are used it may not be necessary to achieve complete absence of ischaemia, since an acceptable degree of improvement may indicate success. What is acceptable may vary with the clinical situation, the age of the patient, and other factors, but normally would exclude a stress test that is so strongly positive that it could indicate the likelihood of subsequent cardiac events such as myocardial infarction or sudden death.[22–24]

In patients with evolving acute myocardial infarction the clinical success of angioplasty should primarily be determined by the degree to which the damage done to the left ventricle is limited. This can be measured to some extent by evaluating by echocardiography or angiography the improvement in left ventricular function in the week or two after the infarction. Additionally, the degree to which spontaneous or stress induced postinfarction angina can be reduced or eliminated may be an important part of the clinical assessment of the success of an angioplasty procedure.[25]

Long term success

The long term success of an angioplasty procedure largely depends on the development of restenosis, which has been shown to occur in up to 35% of cases after a first procedure. This is a separate issue from primary success and initial clinical success. The rate of recurrence depends on several factors including the residual stenosis and the gradient at the end of the initial procedure,[18 26] but it also depends on the criteria by which restenosis is judged. Purely angiographic criteria such as stenosis of ⩾50% at follow up angiography,[4 26] or loss of 50% of the gain achieved at the initial angioplasty,[6 11 26] or increase of stenosis by ⩾30% of the luminal diameter achieved after angioplasty[6] suffer form the drawbacks of not being directly related to the functional state of the patient or the functional importance of the individual stenosis and also from difficulties with accurately measuring the diameter stenosis. Ideally, the term restenosis should only be applied when there is objective evidence of ischaemia by stress testing or other means—as with the initial angioplasty procedure. Analysis of important cardiac events such as myocardial infarction or bypass surgery may also be important in the assessment of long term results,[27] particularly in multivessel disease.[9 11 12 28] The completeness of revascularisation can have a considerable impact on follow up.[9] After single vessel angioplasty of the "culprit" or "target" lesion some patients can maintain a long term clinical improvement despite multivessel disease and unstable angina.[12]

Coronary artery bypass surgery is usually the main alternative treatment to angioplasty and one important criterion of early and long term success may be the avoidance of such an operation. If dilatation does not sufficiently improve symptoms or if significant objective evidence of ischaemia remains the patient will require bypass surgery and angioplasty has clearly been a failure. On the other hand, if repeat angioplasty eliminates the symptoms and the objective evidence of ischaemia the initial procedure might be regarded as a partial success since the procedure as a whole has produced the desired effect. This type of analysis of the value of percutaneous transluminal coronary angioplasty as compared with coronary bypass surgery may be particularly important for multivessel disease.[11] Until now there have been no valid randomised studies comparing angioplasty with bypass surgery, although such studies are clearly needed for an overall assessment of the value of angioplasty. The results of the multicentre study currently being set up for multivessel disease by the National Institutes of Health are eagerly awaited.

References

1 Gruentzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979;301:61–8.

2 Anderson HV, Roubin GS, Leimgruber PP, Douglas JS, King SB, Gruentzig AR. Primary angiographic success rates of percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1985;56:712–7.

3 Leimgruber PP, Roubin GS, Hollman J, *et al.*

Restenosis after successful coronary angioplasty in patients with single-vessel disease. *Circulation* 1986; 73:710–7.

4 Sowton E, Timmis AD, Crick JCP, Griffin B, Yates AK, Deverall P. Early results after percutaneous transluminal coronary angioplasty in 400 patients. *Br Heart J* 1986;56:115–20.

5 Kent KM, Bentivoglio LG, Block PC, *et al.* Percutaneous transluminal coronary angioplasty: report from the Registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol* 1982;49:2011–20.

6 DiSciascio G, Vetrovec GW, Cowley MJ, Wolfgang TC. Early and late outcome of percutaneous transluminal coronary angioplasty for subacute and chronic total coronary occlusion. *Am Heart J* 1986; 111:833–9.

7 Cowley MJ, Vetrovec GW, DiSciascio G, Lewis SA, Hirsh PD, Wolfgang TC. Coronary angioplasty of multiple vessels: short-term outcome and long term results. *Circulation* 1985;6:1314–20.

8 Faxon DP, Kelsey SF, Ryan TJ, McCabe CH, Detre K. Determinants of successful percutaneous transluminal coronary angioplasty: report from the National Heart, Lung, and Blood Institute Registry. *Am Heart J* 1984;108:1019–23.

9 Mabin TA, Holmes DR Jr, Smith HC, *et al.* Follow-up clinical results in patients undergoing percutaneous transluminal coronary angioplasty. *Circulation* 1985; 71:754–60.

10 Hartzler GO, Rutherford BD, McConahay DR, *et al.* Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. *Am Heart J* 1983;106: 965–73.

11 Myler RK, Topol EJ, Shaw RE, *et al.* Multiple vessel coronary angioplasty: classification, results and patterns of restenosis in 494 consecutive patients. *Cathet Cardiovasc Diagn* 1987;13:1–15.

12 Wohlgelernter D, Cleman M, Highman HA, Zaret BL. Percutaneous transluminal coronary angioplasty of the "culprit lesion" for management of unstable angina pectoris in patients with multivessel coronary artery disease. *Am J Cardiol* 1986;58:460–4.

13 Detre KM, Wright E, Murphy ML, Takaro T. Observer agreement in evaluating coronary angiograms. *Circulation* 1975;52:979–86.

14 Wijns W, Serruys PW, Simoons ML, *et al.* Predictive value of early maximal exercise test and thallium scintigraphy after successful percutaneous transluminal coronary angioplasty. *Br Heart J* 1985;53:194–200.

15 Gerbrands JJ, Reiber JHC, Booman F. Computer processing and classification of coronary occlusions. In: Gesema ES, Kanal LN, eds. *Pattern recognition in practice*. New York: North Holland, 1980:223.

16 Ilsley CDJ, Ablett MB. Percutaneous transluminal coronary angioplasty—results in patients with multiple coronary stenoses [Abstract]. *Br Heart J* 1985; 54:627–8.

17 O'Neill WW, Timmis GC, Bourdillon PD, *et al.* A prospective randomized clinical trial of intracoronary streptokinase versus coronary angioplasty for acute myocardial infarction. *N Engl J Med* 1986;314:812–8.

18 Anderson MV, Roubin GS, Leimgruber PP, *et al.* Measurement of transtenotic pressure gradient during percutaneous transluminal coronary angioplasty. *Circulation* 1986;73:1223–30.

19 O'Neill WW, Walton J, Bates ER, *et al.* Criteria for successful coronary angioplasty as assessed by alterations in coronary vasodilatory reserve. *J Am Coll Cardiol* 1984;3:1382–90.

20 Rosing DR, van Raden MT, Mincemoyer RM, *et al.* Exercise, electrocardiographic and functional responses after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1984;53: 36C–41C.

21 Williams DO, Riley RS, Singh AK, Most AS. Coronary circulatory dynamics before and after successful coronary angioplasty. *J Am Coll Cardiol* 1983;1: 1268–72.

22 Ellestad MH, Wan MKC. Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. *Circulation* 1975;51: 363.

23 McNeer JF, Margolis JR, Lee KL, *et al.* The role of the exercise test in the evaluation of patients for ischaemic heart disease. *Circulation* 1978;57:64–70.

24 DeBusk RF, Davidson DM, Houston N, Fitzgerald J. Serial ambulatory electrocardiography and treadmill exercise testing after uncomplicated myocardial infarction. *Am J Cardiol* 1980;45:547–54.

25 Fung AY, Lai P, Juni JE, *et al.* Prevention of subsequent exercise-induced preinfarct ischaemia by emergency coronary angioplasty in acute myocardial infarction: comparison with intracoronary streptokinase. *J Am Coll Cardiol* 1986;8:496–503.

26 Serruys PW, Geuskens R, de Feyter P, *et al.* Incidence of restenosis 30 and 60 days after successful PTCA: a quantitative coronary angiographic study in 200 consecutive patients [Abstract]. *Circulation* 1985; 72(suppl III):III–140.

27 Gruentzig AR, Schlumpf M, Siegenthaler W. Long-term results after coronary angioplasty [Abstract]. *Circulation* 1984;70(suppl II):II–323.

28 Cowley MJ, Vetrovec GW, DiSciascio G, Lewis SA, Hirsh PD, Wolfgang TC. Coronary angioplasty of multiple vessels: short term outcome and long term results. *Circulation* 1985;72:1314–20.

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Congestive cardiac failure: central role of the arterial blood pressure

St Cyres lecture 1986

PETER HARRIS

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SUMMARY A review of the history of our knowledge and understanding of the peripheral oedema of congestive cardiac failure points to the conclusion that an inability of the heart to maintain the arterial pressure is of central importance in this condition. Although the function of the circulation is to perfuse the tissues, the body monitors the adequacy of its perfusion, not through metabolic messengers carried from the tissues in the blood stream, but by sensing the arterial pressure; and the mechanisms evoked act to maintain the arterial pressure. In the short term this is achieved by autonomic regulation of the heart and blood vessels; in the longer term the arterial pressure is maintained through an increase in the blood volume by a retention of salt and water by the kidney. To support the latter process, intrinsic renal mechanisms are successively magnified by the renin—angiotensin—aldosterone system and by the activities of the sympathetic system and vasopressin. The natriuretic influence mediated through volume receptors and the release of atrial peptide is overruled by the arterial baroreceptors, so that the body maintains the arterial pressure at the expense of an increase in blood volume.

In these ways the syndrome of congestive cardiac failure may be regarded as one which arises when the heart becomes chronically unable to maintain an appropriate arterial pressure without support.

Early concepts of cardiac failure

Hope was probably the first to put forward a unified concept of backward failure.[1] It was a concept based on pathology as well as physiology. The overworked ventricle first hypertophies and then dilates. As it dilates the blood gets dammed up behind it and an increased venous pressure is transmitted ultimately to the capillaries where oedema is formed.

The concept of backward failure was widely accepted until the last decade of the nineteenth century. But, in 1896, Starling, in his Arris and Gale lecture, reported experiments on dogs in which he injected oil into the pericardial sac.[2] As the heart "failed" the pressure in the vena cava rose and that in the aorta fell. To decide whether this was accompanied by engorgement of the capillaries he placed a plethysmograph round one limb. This showed unequivocally that the volume diminished at the same time as the aortic pressure decreased and the vena caval pressure increased.

Starling concluded that in failure, although the pressure in the great veins rose, the pressure in the capillaries fell. If that were so, the only explanation that he could see for the loss of liquid from the blood into the tissues was an increased permeability of the capillaries; and the reason for their increased permeability had to be a loss of nutrition due to poor perfusion. "In heart disease the capillary pressure is not higher, but rather lower, than in a normal animal. The dropsy is entirely conditioned by the state of the capillary wall."

This theory of forward failure was championed by Mackenzie: "The blood passes through the capillaries at a slow rate, impairs their nutrition, and allows transudation to take place, which we call dropsy." So strongly did the great physician feel on this subject that there is an entry "Heart failure, back-pressure theory, evil of," in the third edition of his textbook. "These views are the outcome of the discovery of auscultation," he writes, adding that in his

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opinion that discovery had "so far done more harm than good."[3]

In the years that followed, attempts to investigate capillary permeability with dyes failed to demonstrate any increase during cardiac failure. Measurements of the protein composition of oedema liquid found that it was no different from normal interstitial liquid. And direct measurements of capillary pressure by the technique of Landis eventually showed that it was increased in cardiac failure.[4] The normal pressure in digital capillaries held at the level of the heart fell from about 35 mm Hg in the arteriolar limb to about 12 mm Hg in the venous limb. In patients with congestive cardiac failure the pressure in the venous capillary limb averaged around 33 mm Hg.

The blood volume

The argument went literally backwards and forwards but by the second world war, when I became a medical student, backward failure was the standard teaching in London. And yet, looking back on notes which I made at the time, it did not seem to be a complete explanation. The circulation could be divided into two portions: the pulmonary and the systemic. Failure of one ventricle meant simply that blood was transferred from the portion in front of it to the portion behind it. The problem was that the volume of the systemic portion was ten times that of the pulmonary. In the case of the left ventricle, it was easy to imagine how blood transferred from the systemic portion could flood the pulmonary portion. But, when the right ventricle failed, the most that could be transferred into the systemic portion was the total volume of the pulmonary portion, estimated to be less than a pint. In no way could that account for the many pints of anasarca that, in those days, were removed by Southey's tubes.

Oedema of the lungs was, therefore, a special case. It could occur rapidly and could be readily explained on mechanical grounds. The problem was, and is, the slowly developing oedema of the rest of the body which is still generally referred to as right ventricular failure—this is the subject to which I shall address my comments during the remainder of this paper.

Another problem, pondered over in my notes, was the total blood volume. "Plethoric", all the old clinical masters had said. But if either the backward or the forward theory were correct the blood volume should diminish. Evidence suggesting the opposite had been accumulating since the first world war[5] and was greatly supported by Wollheim's extensive measurements.[6]

Early in the second world war Isaac Starr published the work that seemed to point in the right direction. He made a mechanical model which consisted of two pumps, designed to obey Starling's law, connected by pulmonary and systemic circuits the volume and resistance of which could be adjusted.[7] He found that when he made one or both of the pumps "fail" he could reproduce the haemodynamic effects of cardiac failure only if he increased the circulating volume or diminished the circulatory capacity. From this he elaborated his theory of the "static" pressure in the circulation—the pressure which existed throughout the circulation when the pumps were stopped. Extending these ideas to man he found that the "static" pressure measured in newly dead corpses was much higher when there had been cardiac failure.[8]

Starr's observations strongly supported the evidence that capillary pressure was raised in congestive failure. But at the same time they showed that the "static pressure" in a person without congestive failure was lower than the pressure in the venous limb of the capillaries, which lent support to Starling's conclusion that when the cardiac output was abruptly reduced the capillary pressure fell.

Starling's conclusion also receives support from a commonplace observation. At the time of death the heart stops completely and yet tissue oedema does not occur in the succeeding hours even in the areas, for instance, round the eyes, where the tissue is lax and liable to accumulate liquid easily. This state of affairs is explained by a "static pressure" which is considerably lower than the colloid osmotic pressure of the plasma.

So Starling was probably right in believing that the capillary pressure fell in his dogs. His mistake was to transfer this observation to patients with cardiac failure. "The dogs deceived him", as East said of Lewis's work on bundle branch block.

The cardiac output

In the history of cardiology the period of the second world war is notable, above all, for the introduction by Cournand and Richards of the technique of cardiac catheterisation; this made immediately available the measurement of the cardiac output more accurately and securely than had previously been possible. Many early studies showed the cardiac output to be reduced in congestive cardiac failure, which would have pleased both the backward and the forward failure theorists. But shortly after came the discovery of a group of conditions that clinically appeared to be associated with congestive cardiac failure but in which the cardiac output was increased. The causes of this "high output failure" included anaemia, thyrotoxicosis, Paget's disease of bone, arteriovenous fistulas, cor pulmonale, and beriberi.

Here was near disaster for the backward failure theorists and a serious dilemma for the forward failure theorists. If failure was caused by a diminished supply of blood to the body how could the same syndrome occur with a greatly increased blood supply? The answer was the definition which, with small changes in wording, appears today in every text book of cardiology: "a state in which the heart fails to maintain an adequate circulation for the needs of the body ..."[9]

Peripheral metabolism

What was left undefined was the nature of the needs of the body. What was this mysterious metabolic requirement, the lack of which led to oedema?

Fuels for cells consist of oxygen, glucose, and fatty acids. Calculations of the turnover rate of these three fuels in the blood show that the turnover rate of oxygen is five or six times as high as that of the other two. Glucose and fatty acids enter the blood through local streams which subsequently join the main flow. Only for oxygen is the point of entry dependent on the total cardiac output. The most critical need of the body referred to in the definition must, therefore, be the need for oxygen.

But if in patients without metabolic disturbances the circulation becomes inadequate to supply the needs of the body it follows that the oxygen uptake is diminished. Yet the early studies using the Fick principle had clearly shown that this was not so.[10]

The law of the heart

History is not one main road and we shall leave the blind alley into which much of the world of cardiology still finds itself and retrace our steps back to 1915—the year of the law of the heart. "... The mechanical energy set free on passage from the resting to the contracted state depends ... on the length of the muscle fibre. This simple formula serves to 'explain' the whole behaviour of the isolated mammalian heart."[11] The simplicity of the law aided by the sheer arrogance of its title gave it an immediate authority. It was widely welcomed by the backward failure supporters although, as we have seen, Starling himself was firmly committed to forward failure. Note how Starling limited it to the isolated heart. This important and severe limitation has been widely disregarded.

The law takes no account of the processes of hypertrophy and dilatation which are so important in clinical disease. It ignores, also, the important role played by the autonomic system. As Hamilton and Richards were later to point out, "Without the coordinating stimulus of the central nervous system and the hormonal control governed by this system, the truly isolated heart seems to vary its pumping function between that of a heart in a normal resting animal and that of a heart in an animal moribund in the last stages of shock."[12]

The autonomic nervous system

The influence of the autonomic nervous system on the heart was, of course, known to Starling, and much of our present understanding of it dates from the nineteenth century. However, it took a surprisingly long time before the relation between Starling's law and sympathetic drive was elucidated. This was the contribution of Sarnoff and Berglund who showed that a heart could develop a whole family of Starling's curves depending on the degree of sympathetic stimulation.[13]

An entirely new step forward was taken by Chidsey, working in Braunwald's laboratory. He showed that the concentration of noradrenaline in the plasma increased much more in patients with congestive failure during exercise than it did in normal people.[14] The daily excretion of noradrenaline in the urine was also increased in these patients.[15]

The influence of the sympathetic system extended not only to the heart but throughout the vascular system. At about this time Donald, Wade, and Bishop were studying the redistribution of blood flow to various regions of the body in cardiac patients.[16] They showed that the redistribution of flow in patients with cardiac failure was similar to the redistribution seen during physical exercise in normal people. It comprised a reduction in blood flow to the kidneys, gut, and skin, with preservation of flow to the myocardium and skeletal muscle. The vasoconstrictor influence of the sympathetic system on the renal circulation is especially important. In heart failure the increased sympathetic activity causes the renal blood flow to decrease disproportionately to the cardiac output.

Control of the cardiovascular system by the central nervous system

In 1870 Dittmar, working in the laboratories of the self-effacing Carl Ludwig, found that the increase in blood pressure caused by stimulation of the sciatic nerve was retained in animals with pontine transection but abolished when the medulla was destroyed.[17] Owsjannikow, from the same laboratory, studied successive transections of the brain stem and discovered that the blood pressure began to fall at the caudal border of the inferior colliculi and reached the low pressure of a spinal animal with transections below the obex.[18] Dittmar's further studies located the region responsible for maintenance of the blood pressure in the ventral region of the lateral reticular formation.[19]

Later researches have shown a widespread involvement of the reticular formation of the brain stem in the coordination and modulation of cardiovascular responses, and this led to the general view that vasomotor control was diffusely mediated rather than located in a specific area. Recent findings have, however, indicated a specific and important role of a region in the ventrolateral medulla—the site first proposed by Dittmar over a hundred years ago. The first clue came from observations that the application of a cold probe[20] or pharmacological agents[21 22] to a specific area of the ventrolateral surface of the medulla could cause a precipitous fall in blood pressure. These observations suggested the existence of a minute localised vasomotor region lying very close to the surface of the medulla. Subsequent studies have identified it as the rostral portion of the ventrolateral reticular nucleus, corresponding to a group of adrenaline-synthesising cells usually referred to as C1 neurones.[23] Neurones of the C1 area project to the autonomic neurones of the intermediolateral column of the spinal cord.[24] Electrical or chemical stimulation of the C1 area leads to an increase in arterial pressure and heart rate and increased concentrations of catecholamines and vasopressin in the plasma.[25] Electrolytic lesions of the area cause a fall in arterial pressure to levels similar to those of a spinal preparation.[26] The caudal portion of the ventrolateral reticular nucleus consists of cells which contain noradrenaline (A1 area). They project to more rostral cardiovascular regions, including the C1 area and have a depressant effect on the blood pressure.[27 28]

At the beginning of this century, afferent fibres travelling in the vagus and glossopharyngeal nerves were traced to the nucleus tractus solitarius.[29] In 1932 Bronk and Stella demonstrated the existence of the baroreceptors which sense the stretch of the arch of the aorta and the carotid sinus caused by the arterial blood pressure.[30] The afferent baroreceptor impulses end in the nucleus tractus solitarius from which controlling relays pass to the C1 area of the ventrolateral medulla to inhibit its tonic discharge to the preganglionic sympathetic neurones of the intermediolateral column of the spinal cord. At the same time relays pass from the nucleus tractus solitarius to the nucleus ambiguus and the dorsal nucleus of the vagus from which parasympathetic influences are projected through the vagus nerve. In this way, an increased arterial pressure reflexly diminishes cardiovascular sympathetic tone and, at the same time, stimulates parasympathetic activity to slow the heart.

Similar stretch receptors, the "cardiopulmonary volume receptors", give rise to afferent discharges which also travel through the vagus to the nucleus tractus solitarius. These are stimulated by distension of the atrium and other low pressure regions and act to inhibit the sympathetic outflow from the medulla.

Control of the heart rate, cardiac output, and blood pressure is mediated also by regions of the mid-brain, hypothalamus, and cerebral cortex, some of which have been described together by Hilton as organising the "defence reaction."[31] This physiological response is made up of an increased arterial pressure with an increased cardiac output, vasoconstriction in the gut, skin, and kidney, and vasodilatation in skeletal muscle.

Neuroendocrine mechanisms

The relation between the hypothalamus and the pituitary is central to the neuroendocrine control of the body. The posterior pituitary is an extension of the brain into which magnocellular neurones from the paraventricular and supraoptic nuclei descend, carrying oxytocin and vasopressin. Vasopressin has both antidiuretic and vasoconstrictive properties, although the effects of the latter on the arterial pressure are normally concealed by the action of the baroreceptors. In addition to its magnocellular population, the paraventricular region of the hypothalamus contains many parvocellular neurones. Some of these project to the median eminence[32] and are presumably concerned with the neural control of anterior pituitary hormone secretion through the hypophysial long portal system. Other parvocellular neurones of the paraventricular nucleus project to the nucleus tractus solitarius, the ventrolateral medulla, and directly to the intermediolateral column of the spinal cord.[33–35] There are reciprocal connections between the paraventricular nucleus and the nucleus tractus solitarius and A1 area[36] and, through these, the paraventricular nucleus may modulate the baroreceptor arc.

Many peptides are synthesised within the central nervous system. Several of them, including angiotensin II, vasopressin, neurotensin, calcitonin gene-related peptide, and neuropeptide Y, have powerful vasomotor effects elsewhere in the body, but their function in the brain is largely unknown. The blood-brain barrier is, in general, impervious to peptide molecules in the plasma, but, in certain small areas of the ventricular system, the capillary endothelial cells are fenestrated. These "circumventricular" organs may, therefore, be a pathway through which plasma peptides, such as angiotensin II and vasopressin, can influence the central nervous system.

In addition to the influence of the hypothalamus on the release of anterior and posterior pituitary hormones the central nervous system exercises a control over the release of renin from the kidney (either directly through β receptors in the afferent arteriole or indirectly through renal arterial vasoconstriction) and over the release of adrenaline and noradrenaline from the adrenal medulla.

Modifications of the autonomic nervous system

Evidence has been put forward that the baroreceptor response is diminished in patients with heart failure.[37 38] A similar apparent diminution in baroreceptor response has been reported in normal people during exercise.[39 40] In both cases it seems likely that this is an expression of a new setting of the medullary centres which diminish vagal outflow at the same time as they increase sympathetic outflow.

Changes in the autonomic system also occur in the heart itself. There is a diminished response of afferent nerve fibres to stretch in the atrium[41] which may be due to an increased rigidity of the atrial wall or changes in the structure of the afferent endings.[42] A notable change in the myocardium is a profound decrease in the content of noradrenaline.[43-45] Its cause has been debated (see Rupp and Jacob[46] for review). In our experiments (unpublished data) the diminution in content has been specifically associated with failure. In the presence of ventricular hypertrophy without failure the content of noradrenaline has remained unchanged while its concentration has decreased simply because the volume of myocytes has increased. The response of the ventricle to postganglionic sympathetic nerve stimulation has been found to be reduced in dogs with cardiac failure.[47] This may in part be due to the diminished stores of noradrenaline but there is also evidence that there is a decrease in the density of β adrenergic receptors in the myocardium.[48]

The kidneys

Soon after Starr's observations on "static pressure" Warren and Stead followed the course of events in patients with heart failure whose cardiac treatment had been stopped.[49] They found that the body weight and plasma volume started to increase before they could detect any increase in venous pressure. By now it was clear that the formation of oedema and the expansion of the plasma volume implied an increase in the volume of the extracellular space. It is remarkable how long it took for this simple fact, so obvious to anyone who had seen the patients bloated with oedema, to become formally part of the concept of failure.

Now, therefore, attention swung to the kidney. The scanty concentrated urine had been known since the time of Hippocrates and the routine testing for "chlorides" in the urine with silver nitrate had long been used to teach students that chloride was being retained. Merrill showed that the retention of sodium in the urine was associated with a striking diminution in the renal blood flow.[50] "Evidence of 'forward failure' as primary cause of edema" is the subtitle of the paper. But now "forward failure" refers to the kidneys not to vascular endothelium.

At first it was thought that a simple decrease in glomerular filtration rate in the presence of normal tubular reabsorption was sufficient to account for the retention of sodium[51] but more a careful mathematical analysis showed that there was a mysterious increase in tubular reabsorption.[52 53]

In fact, the decrease in glomerular filtration was less than the decrease in renal blood flow and was not obvious until cardiac failure became clinically severe.[52] In dogs with constriction of the thoracic inferior vena cava, glomerular filtration was actually increased in the presence of severe sodium retention.[54] This was unlike what was known to happen when perfusion diminished in the isolated kidney.[55] Here, renal blood flow and glomerular filtration were both maintained as the perfusion pressure was reduced from 180 to 80 mm Hg while below that pressure glomerular filtration fell more precipitously than renal blood flow so that the filtration fraction decreased. The high filtration fraction of cardiac failure implied that the post-glomerular vascular resistance was increased disproportionately to the pre-glomerular resistance. Barger suggested that this would lead to an increased colloid osmotic pressure in the peritubular capillaries which would promote tubular reabsorption of salt and water.[56] This mechanism (originally conceived by Carl Ludwig[57]) did not receive immediate acceptance; but subsequent work has led to the view that it is an important factor regulating reabsorption from the proximal tubule and there is evidence that it functions in this way in congestive cardiac failure.[58 59]

There is in addition abundant evidence of enhanced distal reabsorption of sodium both in high output failure[60 61] and in low output failure.[62-64] This is the region where aldosterone and, probably, atrial natriuretic factor exert their effects.

Renin-angiotensin-aldosterone

The first clue to the importance of aldosterone in cardiac failure was found by Singer and Werner who observed that the urine of patients with failure contained a sodium-retaining substance.[65] This was soon identified as aldosterone.[66] Evidence of an increased secretion of aldosterone into the blood grew both in patients and in experimental animals.[67] When one adrenal was removed and the other transplanted to the neck the response of aldosterone to constriction of the thoracic inferior vena cava was normal.[68] Crossed circulation of blood from a dog with a constricted vena cava to a normal dog caused an increased secretion of aldosterone.[69] These studies showed that the stimulus to the secretion of aldosterone was humoral. Further studies with nephrectomy and the injection of renal extracts showed that the agent came from the kidney, and it was only a short step to identify it as renin and the immediate humoral agent as angiotensin II.[70] In fact Merrill and his colleagues had already reported an increased concentration of renin in renal venous blood of patients in cardiac failure in 1946, but its significance had gone unrecognised.

The increased release of renin during renal ischaemia had been known since Goldblatt *et al*'s original observations.[71] Now this mechanism could be seen to be operating in cardiac failure. However, although the renal blood flow was known to be decreased in cardiac failure, the control of the release of renin from the juxtaglomerular cells was found to depend on the mean arterial perfusion pressure rather than on blood flow.[72] This supported Tobian *et al*'s theory that the release of renin was directly regulated by the degree of stretch of the walls of the afferent glomerular arterioles[73]; subsequent work has confirmed this mechanism. In addition, changes in the concentration of sodium chloride ions in the region of the macula densa affect the rate of release of renin. This mechanism underlies the effects of a dietary restriction of salt and of diuretics which act by inhibiting the reabsorption of chloride in the ascending limb of the loop of Henle. The direct effects of perfusion pressure, however, can be shown to operate when the macula is excluded.[74]

The relation between renal arterial pressure and plasma renin activity shows that little renin is released as the mean renal arterial pressure falls from 100 to 85 mm Hg.[75] Thereafter the increase in plasma renin activity increases linearly down to pressures of 50 mm Hg. This implies that the intrinsic afferent arteriolar stretch receptor system is, by itself, relatively unresponsive to a small fall in arterial pressure. The responsiveness of the system is, however, greatly increased by adrenergic stimuli, which act by increasing the threshold for renin release[75] so that a small decrease in arterial pressure can evoke a substantial release of renin. Both stimulation of renal sympathetic nerves and bloodborne adrenergic agents are effective and act through β receptors.

Electrical stimulation of the dorsolateral pons[76] and the lateral hypothalamus[77] evoke renin release that can be prevented by denervation of the kidneys. The afferent limb of the reflex arises from the arterial baroreceptors and the cardiopulmonary "volume" receptors described above.[78] The two systems may be shown to conflict under experimental conditions[79] and, as discussed later, presumably do so in cardiac failure.

The operation of the sympathetic system is not necessary for the release of renin by the kidney in response to a decreased perfusing pressure but renin release is greatly enhanced by sympathetic stimulation. Thus the reflex control of the release of renin seems to be particularly important when arterial pressure changes slightly with physiological conditions such as posture[80] and exercise.[81] Even psychological stimuli have been found to increase plasma renin activity.[82] Careful early studies had shown that the sympathetic system, the baroreceptors, and volume receptors and even the brain were not necessary to the renin-aldosterone response during constriction of the thoracic inferior vena cava in animals.[67] This gave rise to the view that the nervous system was not a factor. But something which is not necessary may still be used, and the present evidence suggests that the nervous system has an important role in human disease in which the initial degrees of cardiac disability are likely to be less severe.

In addition to stimulating the secretion of aldosterone, angiotensin II has other important properties in cardiac failure; it is a powerful vasoconstrictor, it enhances adrenergic neuroeffector transmission, and it is concerned with the sensation of thirst. Its constrictor properties are important in maintaining the arterial pressure and may be the cause of the particular increase in post-glomerular vascular resistance.[83]

Early measurements of both aldosterone and renin activity in the plasma were confusing. It seemed that both were increased in some patients but were normal in others. The explanation came from the experiments on dogs carried out by Watkins *et al.*[84] They showed that after constriction of the pulmonary artery or inferior vena cava "the initial response was a reduction in blood pressure, a rise in plasma renin activity, plasma aldosterone, and water intake, and nearly complete sodium retention. In the days after moderate constriction plasma volume and body weight increased (with development of ascites and oedema); blood pressure, sodium excretion, plasma renin activity, and plasma aldosterone returned to normal. In animals in which blood pressure was not restored, plasma renin activity and plasma aldosterone remained elevated throughout the period of constriction."

This view of the endocrine response as something which might be transient, rather than sustained, was an important step forward. The renin-angiotensin-aldosterone system responds both in low output and in high output failure[85] and the considerable number of reports on the beneficial effects of converting enzyme inhibitors testifies to the great importance of this system in clinical cardiac failure.

Arginine vasopressin

Early studies showed that the urine of patients with cardiac failure contained an antidiuretic substance[86 87] but it was some years before analytical techniques were adequate to show that plasma vasopressin concentration was increased.[88] This finding was consistent with the highly concentrated urine passed in cardiac failure, and the studies of Anderson *et al* showed the role of vasopressin and the mechanism through which its release is stimulated.[89] Their experiments were carried out on dogs subjected to acute obstruction of the thoracic inferior vena cava. If the renal arterial pressure was held constant there was a fall in cardiac output and aortic pressure, a fivefold increase in urinary osmolality, and a dramatic reduction in free water clearance. Hypophysectomy greatly attenuated the response of urinary osmolality and free water clearance if renal arterial pressure was held constant but, if renal arterial pressure was allowed to fall, there was a considerable decrease in free water clearance. From this it could be concluded that the increase in urinary osmolality was due almost entirely to vasopressin, while the decreased free water clearance was also partly determined by a diminished delivery to the distal nephron. Constriction of the inferior vena cava had no effect on urinary osmolality or free water clearance in dogs that had intact hypophyses but denervation of the baroreceptors. This indicated that the release of vasopressin during vena caval constriction was stimulated by a reduction in afferent baroreceptor impulses.

Constriction of the inferior vena cava, however, is unlike intrinsic failure of the heart in that the pressures affecting the low-pressure "volume" receptors are diminished.[84] The studies of Anderson *et al*[89] therefore suggest that in patients with cardiac disease the stimulatory effect of a low arterial pressure on the release of vasopressin overrides the inhibitory effect of atrial distension. Such a predominance of arterial baroreceptors over atrial stretch receptors appears to be normal in primates.[90 91] It is unlikely that the increased release of vasopressin in congestive failure is mediated through osmoreceptors since the plasma osmolality is generally decreased rather than increased.

Atrial natriuretic peptide

Early electron microscopical studies had shown the presence of specific granules in atrial myocytes, but their function was not suspected until de Bold showed that the numbers of granules varied with changes in water and electrolyte balance.[92] Two years later he showed that atrial extracts had a natriuretic effect.[93]

The active principle has now been identified as a polypeptide and its amino acid sequence has been determined.[94 95] In the atrium it appears to be formed from the cleavage of a larger precursor molecule.[96] Atrial natriuretic peptide is released in response to a high atrial pressure[97] and the plasma concentration of the peptide has been found to be increased in patients with congestive cardiac failure.[98]

The natriuretic effect appears to be located in the distal tubules and collecting ducts.[99] In the whole animal the effects of the peptide may be partly mediated through an inhibition of the secretion of aldosterone and of the release of renin. In addition to its effects on the kidney, atrial natriuretic peptide has been shown to be a vasodilator.[100]

Distention of the atrium causes a release of natriuretic peptide and at the same time stimulates nerve receptors that lead to an inhibition of sympathetic activity and a diminished release of renin. The two mechanisms, therefore, act together to lower systemic vascular resistance and increase the excretion of sodium. But, clearly, the natriuretic and vasodilator effects of the peptide in patients with cardiac oedema are quite outweighed by the sodium retention and vasoconstriction caused by sympathetic stimulation and activation of the renin-angiotensin-aldosterone system. It follows also that the stimulation of the sympathetic-renin-angiotensin-aldosterone system by the low arterial pressure outweighs its inhibition by cardiopulmonary volume receptors.

Retention of saline is harmful

It may be supposed that the body reacts to a failing heart in a manner which will be beneficial. For instance, the retention of water by the kidneys may be seen as a way of increasing the filling of the heart and, thereby, its output. And yet diuretics are probably the most efficacious treatment we have. Vasoconstriction should maintain the blood pressure and preserve flow to vital organs. Yet vasodilators are now widely used to treat cardiac failure. Similarly it might be argued that angiotensin II and aldosterone are beneficial; yet captopril and spironolactone are found to be helpful.

It seems that every time we thwart nature's intentions, the patient improves. The explanation of this paradox is that the processes which are evoked during cardiac failure originally evolved for some quite different purpose.[101]

Cardiac failure is a rare event. So exotic a condition would not have any perceptible effect on the survival of the species. The powerful mechanisms that we find in cardiac failure are more likely to have evolved to deal with circumstances vital to everyday preservation. Of these circumstances the two most obvious are physical exercise and trauma.

Unpublished studies carried out with colleagues at the University of Brescia have shown that during exercise plasma concentrations of several hormones increase in a sequential fashion: noradrenaline and adrenaline, vasopressin, and atrial natriuretic peptide, followed by renin activity and aldosterone. Measurements on patients with untreated myocardial infarction also showed an increase in all these factors.

The neuroendocrine-renal response in both these conditions is, therefore, similar to the response in congestive cardiac failure. The important difference is in the length of time over which the stimulus is maintained—minutes or hours for exercise, hours or days for shock, weeks or months or years for cardiac failure. The mechanisms that may be necessary for exercise or for survival in injury are harmful when maintained over prolonged periods because they lead to the retention of saline in the body. For the reason why the excessive retention of saline is harmful we have to go back far into evolutionary history to the emergence of air-breathing animals[101] since it is the air-breathing lung that is so susceptible to flooding.

Cardio-neuro-endocrine links

Apart from the complicating presence of pain, the condition of acute myocardial infarction is a highly appropriate model of the immediate neuro-humoral response of the body to a suddenly diminished pumping capacity of the heart. Already there is evidence of both increased sympathetic activity and its associated endocrine response.

We have already discussed the links between a stimulation of the sympathetic system and the endocrine response. But what is the link between a diminished cardiac output and the stimulation of the sympathetic system?

There appear to be two main possibilities: metabolic and mechanical. First, the low cardiac output may lead to underperfusion of the tissues that release some intermediary substance into the blood stream. Second, the purely mechanical effects of a low cardiac output may give rise to the requisite afferent impulses.

Is there ischaemia of the tissues in cardiac failure? We can say, as noted above, that the oxygen uptake of the body is undiminished at rest in congestive failure; but the oxygen content of the mixed venous blood is abnormally low so that, in general, the tissues must be functioning at a lower Po_2 than normal. Nevertheless, the blood lactate in such patients is normal at rest[102] and we can, therefore, conclude that, at rest, the supply of oxygen is not rate-limiting for ATP synthesis in the body as a whole.

On the other hand, the concentration of lactate in the blood increases to a greater extent than normal during exercise in cardiac patients.[102] This may, in part, be due to the glycolytic action of catecholamines (whose presence in excess during exercise of patients with cardiac failure has already been discussed) and in part to an inadequate supply of oxygen. In the latter case, it might be reasonable to suppose that a metabolic messenger was released into the blood stream and stimulated either the heart or the central nervous system at some distant point.

Experimental evidence, however, is entirely against such a hypothesis. First, the increase in heart rate occurs within a cardiac cycle,[103] an interval much shorter than the circulatory time required for the messenger. Second, substantially the same increase in heart rate and arterial pressure occurs in normal subjects whether or not the exercising limb is rendered ischaemic.[104-106]

There are, however, two organs in which a reduction in blood flow may have a specific effect—the kidney and the brain. A decrease in renal perfusion pressure associated with a reduced cardiac output may itself stimulate the release of renin and favour the retention of saline by the kidney. The reduction of renal blood flow in cardiac failure is, however, proportionally greater than the reduction in cardiac output.[16] This is an indication of the importance of the increased sympathetic activity which magnifies the release of renin, as discussed above. A further, and little considered, result of a reduced renal blood flow may be an increased production of erythropoietin, since there is an increase in total red cell volume as well as plasma volume in cardiac failure.[107]

The vasopressor effects of severe ischaemia of the brain stem have been known since the last century. These effects have been shown to be mediated through the rostral ventrolateral medulla; lesions in this area abolish the effects.[108] Cerebral blood flow tends to be protected in cardiac failure[16] and brain stem ischaemia has to be severe to have vasopressor effects, so that the operation of this mechanism in cardiac failure remains uncertain.

In the original experiments of Alam and Smirk[104 105] discussed above, both the heart rate and the arterial pressure remained raised after exercise so long as the cuff stopping blood flow was inflated. Subsequent investigators have confirmed this observation with regard to the blood pressure but not always with regard to the heart rate.[109] Alam and Smirk suggested that the afferent impulses arose from stimulation by some metabolite released from exercising muscle fibres. Subsequent investigations have pointed to potassium ions as the likely local mediator.[110]

The existence of a reflex mechanism arising from exercising muscles was shown directly in cats by Coote *et al.*[111] Stimulation of the ventral root causing tetanic contractions of the hind limb was accompanied by an increase in the heart rate and arterial pressure. The cardiovascular response was not affected by dividing nerves to neighbouring joints or skin but was abolished by neuromuscular blockade or by cutting the dorsal roots. The afferent impulses travel through small, slowly conducting fibres with free nerve endings.[109 112] Some of these afferent fibres relay directly to the nucleus tractus solitarius[113] and may, therefore, be responsible for the re-setting of the baroreflex arc which allows a moderate increase in arterial pressure during exercise. It will be remembered that Dittmar's experiments showed that the hypertension caused by stimulation of the sciatic nerve was retained despite transection at the level of the pons.[17] In addition to such clear cut evidence of a cardiovascular influence of muscle afferents, there is evidence, albeit less strong, that influences from the cerebral cortex also have a role.[109]

The experiments of Alam and Smirk[105] and others, quoted above, not only demonstrate the existence of a cardiovascular reflex from exercising muscle but also show that this reflex is unaffected by ischaemia of the muscle. There is, therefore, no reason to believe that the increased sympathetic response to exercise in cardiac patients is caused by an increased afferent input to the medullary centres. Cortical and other higher influences may be operating in evoking the defense reaction in these distressed patients. Similarly more general somatosensory afferents (for instance associated with dyspnoea or exhaustion) may have a direct influence on the reticular formation of the brain stem.[114 115] Both these latter influences may act to re-set the central baroreflex mechanism, both during exercise and at rest.

By far the most obvious way, however, in which a reduced cardiac output will magnify the sympathetic outflow, during rest and exercise, is through the vascular stretch receptors. And, here, the influence of the arterial baroreceptors must dominate, since the distension of the cardiopulmonary portion of the circulation will inhibit, rather than stimulate, the sympathetic outflow.

A condition in which the cardiac output is inadequate to maintain the arterial pressure

All these different lines of argument converge on the conclusion that control of the arterial pressure is the key link in the process of congestive cardiac failure. Present day opinion follows the view that in cardiac failure the cardiac output is insufficient for the metabolic needs of the body. But the needs of the body are, as we have seen, being met. Neither is there any evidence that the disturbances in energy pathways which may be required to maintain these needs lead to some blood borne messenger or to any increase in the afferent input from the limbs to the central nervous system.

Of course, the purpose of the circulation must be to provide perfusion to the tissues. But the body assesses the adequacy of the circulation by sensing the arterial pressure and not through metabolic messengers from the tissues. The arterial pressure is sensed by the juxtaglomerular cells and by the baroreceptors, and the sympathetic outflow which results from a reduction of baroreceptor input magnifies the response of the juxtaglomerular cells.

In this way, also, the mechanism of high output failure becomes apparent. All such patients have an abnormally low systemic vascular resistance either from vasodilatation or from arteriovenous shunts. Vasodilatation might be supposed to lead to oedema because the pressure at the arterial end of the capillary may be increased. This may well be a factor in some instances, but it cannot apply to the patients with arteriovenous communications. The common factor is the tendency to low blood pressure. Closure of an arteriovenous fistula causes an increased blood pressure and a prompt natriuresis.[116] The difference between high output and low output failure is the difference in the ability of the heart to respond to the increased sympathetic drive.

Oedema is commonly associated with vasodilator treatment and may also be explained in this way. The oedema of cor pulmonale is always associated with the retention of carbon dioxide, which is a powerful vasodilator. In addition, a raised $P\text{CO}_2$ in the cerebral circulation specifically stimulates the vasomotor sympathetic outflow.

Hypertension and cardiac failure: common ground

Scientific and clinical specialisation alike have led to a world wide separation between those whose interest is primarily the blood pressure and those whose interest is primarily the heart: different societies, different journals. What is astounding is that exactly the same neurohumoral mechanisms are being studied independently by both groups. One group believes that these mechanisms are important in the control of the blood pressure; the other that they are important in cardiac failure. This paradox seems to have gone unremarked but is at once understandable if control of the blood pressure is the determining factor in cardiac failure.

Arterial pressure, cardiac output, and exercise

A look back over evolutionary history shows that the arterial pressure and the cardiac output took a sudden jump together when the warm-blooded animals emerged.[101] With a high cardiac output and a superior air-breathing respiratory apparatus the mammals and birds were able to make full use of the energy available from oxidation in their red muscles. In this way they have developed the surpassing capacity for physical activity which has been a main origin of their success. For this purpose the circulation has to provide for a sudden massive increase in blood supply to the exercising muscles. This is achieved by a great capacity for an increased output and by vasodilatation in the exercising muscle and vasoconstriction in other regions.

I have argued elsewhere that it is these requirements of physical exercise which have necessitated the extraordinarily high arterial pressure of the mammals and birds.[101] The combination of a high resting arterial pressure, together with an immense capacity for vasodilatation in skeletal muscle, allows a sudden massive increase in cardiac output with only a moderate increase in left ventricular emptying pressure. Thus the links between the cardiac output and the arterial pressure are archetypal and have their origins in the requirements for physical activity.

It may not, therefore, be surprising that the effects of physical exercise are specifically important in patients with a limited cardiac output. The therapeutic effect of rest in such patients was well known to our predecessors but has largely been forgotten by a generation obsessed with the cult of physical fitness. Physical exercise, as we have seen, evokes the same neuroendocrine response as is found in cardiac failure and, as judged by the concentration of plasma noradrenaline, the response to physical exercise is especially increased in cardiac patients.

During exercise, as discussed above, afferents from the exercising limbs and, probably, commands from higher centres re-set the medullary cardiovascular control system to permit an increased heart rate and arterial pressure. The diseased heart is unable to increase its output to the normal extent in response to autonomic control. During exercise, therefore, it is unable to increase the arterial pressure to the extent demanded by the medullary control system. The massive and largely locally mediated vasodilatation in the exercising muscles may even lead to a fall in arterial pressure. In the absence of an adequate modulatory baroreceptor input, the inhibitory influence of the nucleus tractus solitarius on the vasomotor elements of the reticular formation and perhaps specifically the C1 area may be presumed to be diminished so that the outflow to the preganglionic sympathetic neurones of the intermediolateral column of the spinal cord is increased.

The neuroendocrine response in congestive failure may well, therefore, be intermittent, according to the state of physical activity of the patient. This would in part explain why isolated blood samples may fail to show abnormal concentrations of hormones and why a chronic re-setting of the baroreceptor arc does not seem to occur.

Finally, it will be noted that all the changes in the peripheral autonomic system, reviewed above, will exacerbate the condition of congestive failure. Diminution of the baroreceptor response will reduce the inhibitory control which this exerts on the vasomotor centres. A decreased responsiveness of atrial receptors will reduce the afferent input whereby a distended atrium reduces sympathetic outflow. A lack of responsiveness of the myocardium to postganglionic sympathetic stimulation will reduce the increase in output that is necessary to maintain the blood pressure.

Conclusion

The evolution of a high cardiac output in the warm-blooded animals has provided a surpassing capacity for physical activity supported by oxygen. The oxygen uptake of exercising muscles is met by a massive capacity for local vasodilatation and by an increase in cardiac output. The co-evolution of a high resting arterial pressure permits the increase in cardiac output to take place during exercise with a relatively stable left ventricular emptying pressure.

Although the function of the circulation is to perfuse the tissues, the body monitors the adequacy of its perfusion, not through metabolic messengers carried from the tissues in the blood stream, but by sensing the arterial pressure. A damaged heart becomes progressively less able to maintain the arterial pressure, at first during exercise and ultimately at rest. When this happens the body responds in the stereotyped manner for which it has been programmed by natural selection to maintain the arterial pressure during exercise or trauma.

In the short term this is achieved by autonomic regulation through the baroreflex arc, the central control of which is modulated by afferents from the limbs and instructions from higher centres. In the longer term the arterial pressure is maintained through an increase in the blood volume by retention of saline by the kidney. To this end local renal mechanisms are successively magnified by the renin-angiotensin-aldosterone system and by the activity of the sympathetic system and vasopressin. In cardiac failure the natriuretic influence mediated through volume receptors and the release of atrial natriuretic peptide is overruled by the arterial baroreceptors so that the body maintains the arterial pressure at the expense of an increase in blood volume.

The increase in blood volume is, therefore, the result of "forward failure". But the distribution of the excess volume of blood is determined by the mechanical forces of "backward failure". Thus both these processes raise the pressure in the peripheral capillaries so that liquid is expelled into the tissue spaces to form oedema.

In these ways the arterial pressure has a central role in congestive cardiac failure and that syndrome may, with little exaggeration, be regarded primarily as one which arises when the heart is chronically unable to maintain an appropriate blood pressure without support.

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References

1 Hope J. *A treatise on the diseases of the heart and great vessels, and on the affections which may be taken for them: comprising the author's view of the physiology of the heart's action and sounds.* London: John Churchill, 1832.

2 Starling EH. On the absorption of fluids from the connective tissue spaces. *J Physiol* 1896;**19**:312–26.

3 Mackenzie J. *Diseases of the heart.* 3rd ed. Oxford Medical Publications, 1913:26.

4 Fahr G, Ershler I. Studies of factors concerned in edema formation. II. The hydrostatic pressure in the capillaries during edema formation in right heart failure. *Ann Intern Med* 1941;**15**:798–810.

5 Keith NM, Rowntree LG, Geraghty JT. A method for the determination of plasma and blood volume. *Arch Intern Med* 1915;**16**:547–76.

6 Wollheim E. Die Zirkulierende blutmenge und ihre bedeutung fur kompensation und dekompensation des kreislaufs. *Z Klin Med* 1931;**116**:269–397.

7 Starr I, Rawson AJ. Rôle of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. I. Theoretical studies on an improved circulation schema whose pumps obey Starling's law of the heart. *Am J Med Sci* 1940;**199**:27–39.

8 Starr I. Rôle of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. II. Clinical and experimental studies. *Am J Med Sci* 1940;**199**:40–55.

9 Wood PW. *Diseases of the heart and circulation.* Philadelphia: Lippincott, 1956.

10 Hickman JB, Cargill WH. Effect of exercise cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J Clin Invest* 1948;**27**:10–23.

11 Starling EH. *The Linacre lecture on the law of the heart given at Cambridge, 1915.* London: Longmans, Green, 1918.

12 Hamilton WF, Richards DW. The output of the heart. In: Fishman AP, Richards DW, eds. *Circulation of the blood. Men and ideas.* New York: Oxford University Press, 1965:71–126.

13 Sarnoff SJ, Berglund E. Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular curves. *Circulation* 1954;**9**:706–18.

14 Chidsey CA, Harrison DC, Braunwald E. The augmentation of plasma norepinephrine response to exercise in patients with congestive heart failure. *N Engl J Med* 1962;**267**:650–4.

15 Chidsey CA, Braunwald E, Morrow AG. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Am J Med* 1965;**39**:442–51.

16 Wade OL, Bishop JM. *Cardiac output and regional blood flow.* Oxford: Blackwell, 1962.

17 Dittmar C. Ein Neurer Beweiss fur die Reizbarkeit de Centripetalen fasern des Ruckenmarks. *Ber Sdchs Ges Wiss* 1870;**22**:18–45.

18 Owsjannikow P. Die tonischen und reflektorischen centren der gefässnerven. *Ber Sàchs Ges Wiss* 1871;**23**:135–47.

19 Dittmar C. Uber die Loge des Sogenannten Gefässcentrums der Medulla Oblongata. *Ber Sàchs Ges Wiss* 1873;**25**:449.

20 Schläfke M, Lóschke HH. Lokalization eines au der regulation von atmung und kreislauf beteiligten gebiets an der ventralen oberfloeche der medulla oblongata durch kalteblockade. *Pflugers Arch* 1967;**297**:201–20.

21 Feldberg W, Guertzenstein PG. A vasodepressor effect of pentobarbitone sodium. *J Physiol (Lond)* 1972;**224**:83–103.

22 Feldberg W, Guertzenstein PG. Vasodepressor effect obtained by drugs acting on the ventral surface of the brain stem. *J Physiol (Lond)* 1976;**258**:337–55.

23 Hokfelt T, Fuxe K, Goldstein M, Johansson O.

Immunohistochemical evidence for the existence of adrenaline neurons in the rat brain. *Brain Res* 1974;**66**:235–51.

24 Ross CA, Armstrong DM, Ruggiero DA, Pickel VM, Joh TH, Reis DJ. Adrenaline neurons in the rostral ventrolateral medulla innervate thoracic spinal cord. *Neurosci Lett* 1981;**25**:257–62.

25 Ross CA, Ruggiero DA, Park DH, *et al.* Tonic vasomotor control by the rostral ventrolateral medulla: effect of electrical or chemical stimulation of the area containing C1 adrenaline neurons on arterial pressure, heart rate and plasma catecholamines and vasopressin. *J Neurosci* 1984;**4**:479–94.

26 Granata AR, Ruggiero DA, Park DH, John TH, Reis DJ. Brain stem area with epinephrine neurons mediates baroreflex vasopressor responses. *Am J Physiol* 1985;**248**:H547–67:

27 Blessing WW, Reis DJ. Inhibitory cardiovascular function of neurons in the caudal ventrolateral medulla of the rabbit: relationship to the area containing A1 noradrenergic neurons. *Brain Res* 1982;**253**:161–71.

28 Imaizumi T, Granata AR, Benarroch EE, Sved AE, Reis D. Contributions of arginine vasopressin and the sympathetic neurons system to the fulminating hypertension after destruction of caudal ventrolateral medulla of the rat. *J Hypertens* 1985; **3**:491–501.

29 Cajal RY. *Histologie du système nerveuse de l'homme et des vertebres*. Vol. 1. Paris: Maloine, 1909.

30 Bronk DW, Stella G. Afferent impulses in the carotid sinus nerve. I. The relation of the discharge from single end organs to arterial blood pressure. *J Cell Comp Physiol* 1932;**1**:113–30.

31 Hilton SM. Central nervous origin of vasomotor tone. *Adv Physiol* 1980;**8**:1–12.

32 Swanson LW. Immunohistochemical evidence for a neurophysin-containing autonomic pathway arising in the paraventricular nucleus of the hypothalamus. *Brain Res* 1977;**128**:346–53.

33 Saper CB, Loewy AD, Swanson LW, Cowan WM. Direct hypothalamic-autonomic connections. *Brain Res* 1976;**117**:305–12.

34 Kannan H, Yamashita H. Connections of neurons in the region of the nucleus tractus solitarius with the hypothalamic paraventricular nucleus: their possible involvement in the neural control of cardiovascular system. *Brain Res* 1985;**329**:205–12.

35 Caverson MM, Ciriello J, Calavesu FR. Cardiovascular afferent inputs to neurons in the ventrolateral medulla projecting directly to the central autonomic area of the thoracic cord in the cat. *Brain Res* 1983;**274**:354–8.

36 Sawchenko PE, Swanson LW. A method for tracing biochemical defined pathways in the central nervous system using combined fluorescence retrogade transport and immunohistochemical techniques. *Brain Res* 1981;**210**:31–51.

37 Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971;**285**:877–83.

38 Higgins CB, Vatner SF, Eckberg DL, Braunwald E. Alterations in the baroreceptor reflex in conscious dogs with heart failure. *J Clin Invest* 1972;**51**:715–24.

39 Eckberg DL, Fletcher GF, Braunwald E. Influence of background autonomic activity upon the response to carotid sinus nerve stimulation in man [Abstract]. *Am J Cardiol* 1970;**26**:631.

40 Bristow JD, Brown EB Jr, Cunningham DJC, *et al.* Effect of bicycling on the baroreflex regulation of pulse interval. *Circ Res* 1971;**28**:582–92.

41 Greenberg TT, Richmond WH, Stocking RA, Gupta PD, Meehan JP, Henry JP. Impaired atrial receptor responses in dogs with heart failure due to tricuspid insufficiency and pulmonary artery stenosis. *Circ Res* 1973;**32**:424–33.

42 Zucker IH, Earle AM, Gilmore JP. The mechanism of adaptation of left atrial stretch receptors in dogs with congestive heart failure. *J Clin Invest* 1977;**60**:323–31.

43 Chidsey CA, Kaister GA, Sonnenblick EH, Spann JF, Braunwald E. Cardiac norepinephrine stores in experimental heart failure in the dog. *J Clin Invest* 1964;**43**:2386–93.

44 Chidsey CA, Braunwald E, Morrow AG. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Am J Med* 1965;**39**:442–51.

45 Chidsey CA, Sonnenblick EH, Morrow AG, Braunwald E. Norepinephrine stores and contractile force of papillary muscle from the failing heart. *Circulation* 1966;**33**:43–51.

46 Rupp H, Jacob R. The autonomic nervous system of the heart. In: Rupp H, ed. *The regulation of heart function*. New York: Thieme, 1986:53–70.

47 Covell JW, Chidsey CA, Braunwald E. Reduction of the cardiac response to postganglionic sympathetic nerve stimulation in experimental heart failure. *Circ Res* 1966;**19**:51–6.

48 Bristow MR, Ginsburg R, Minobe W, *et al.* Decreased catecholamine sensitivity and β-adrenergic-receptor density in failing human hearts. *N Engl J Med* 1982;**307**:205–11.

49 Warren JV, Stead EA Jr. Fluid dynamics in chronic congestive failure. *Arch Intern Med* 1944;**73**:138–47.

50 Merrill AJ. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as primary cause of edema. *J Clin Invest* 1946;**25**:389–400.

51 Mokotoff R, Ross G, Leiter I. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. *J Clin Invest* 1948;**27**:1–9.

52 Briggs AP, Fowell DM, Hamilton WF, Remington JW, Wheeler NC, Winslow JW. Renal and circulatory factors in the edema formation of congestive heart failure. *J Clin Invest* 1948;**27**:810–7.

53 Bradley SE, Blake WD. Pathogenesis of renal dysfunction during congestive heart failure. *Am J Med* 1949;**6**:470–80.

54 Davis JO, Howell DS. Mechanisms of fluid and electrolyte retention in experimental preparations in dogs. II. With thoracic inferior vena cava con-

striction. *Circ Res* 1953;1:171–8.

55 Shipley RE, Study RS. Changes in renal blood flow, extraction of inulin, glomerular filtration rate, tissue pressure and urine flow with acute alterations of renal artery blood pressure. *Am J Physiol* 1951;167:676–88.

56 Barger AC. The pathogenesis of sodium retention in congestive heart failure. *Metabolism* 1956;5:480–9.

57 Ludwig C. Nieren und Hambereitung. In: Wanger R, ed. *Handworterbuch der Physiologie*. Vol. 2. Braunschweig: Vieweg F & Son, 1844:628–59.

58 Cirksena WJ, Dirks JH, Berliner RW. Effect of thoracic cava obstruction on response of proximal tubule sodium reabsorption to saline infusion. *J Clin Invest* 1966;45:179–86.

59 Earley LE, Martino JA, Friedler RM. Factors affecting sodium reabsorption by the proximal tubule as determined during blockade of distal sodium reabsorption. *J Clin Invest* 1966;45: 1668–84.

60 Schneider EG, Dresser TP, Lynch RE, Knox FG. Sodium reabsorption by proximal tubule of dogs with experimental heart failure. *Am J Physiol* 1971;220:952–7.

61 Stumpe KO, Sölle H, Klein H, Krück F. Mechanism of sodium and water retention in rats with experimental heart failure. *Kidney Int* 1973;4:309–17.

62 Auld RB, Alexander EA, Levinsky NG. Proximal tubular function in dogs with thoracic caval constriction. *J Clin Invest* 1971;50:2150–8.

63 Levy M. Effects of acute volume expansion and altered hemodynamics on renal tubular function in chronic caval dogs. *J Clin Invest* 1972;51:922–38.

64 Mandin H. Cardiac edema in dogs. Proximal tubular and renal function. *Can J Physiol Pharmacol* 1979;57:185–92.

65 Singer B, Werner J. Excretion of sodium-retaining substances in patients with chronic heart failure. *Am Heart J* 1953;45:795–801.

66 Axelrod BJ, Cates JE, Johnson BB, Luetscher JA Jr. Aldosterone in urine of normal man of patients with oedema. *Br Med J* 1955;1:196–9.

67 Davis JO. The physiology of congestive heart failure. In: Hamilton WF, Dow P, eds. *Handbook of physiology*. Section 2: vol 3: 2071–122. American Physiological Society, 1965.

68 Carpenter CCJ, Davis JO, Holman JE, Ayers CR, Bahn RC. Studies on the response of the transplanted kidney and the transplanted adrenal gland to thoracic inferior vena caval constriction. *J Clin Invest* 1961;40:196–204.

69 Yankopoulos NA, Davis JO, Kliman B, Peterson RE. Evidence that a humoral agent stimulates the adrenal cortex to secrete aldosterone in experimental secondary hyperaldosteronism. *J Clin Invest* 1959;38:1278–89.

70 Biron P, Koiw E, Nowaczynski W, Brouillet J, Genest J. Effects of intravenous infusion of valine-5-angiotensin II and other pressor agents on urinary electrolytes and corticosteroids, including aldosterone. *J Clin Invest* 1961;40:338–47.

71 Goldblatt H, Lynch J, Hanzel RF, Summercille WW. Studies on experimental hypertension, I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med* 1934;59:347–79.

72 Skinner SL, McCubbin JW, Page IH. Control of renin secretion. *Circ Res* 1964;15:64–76.

73 Tobian L, Tomboulian A, Janacek J. The effect of high perfusion pressure on the granulation of juxtaglomerular cells in an isolated kidney. *J Clin Invest* 1959;38:605–10.

74 Blain EH, Davis JO, Witty RT. Renin release after haemorrhage and after suprarenal aortic constriction in dogs without sodium delivery to the macula densa. *Circ Res* 1970;27:1081–9.

75 Farhi ER, Cant JR, Barger AC. Interactions between intrarenal epinephrine receptors and the renal baroreceptor in the control of PRA in conscious dogs. *Circ Res* 1982;50:477–85.

76 Richardson D, Stella A, Leonetti G, Bartorelli A, Zanchetti A. Mechanisms of renal release on renin by electrical stimulation of the brainstem in the cat. *Circ Res* 1974;34:425–34.

77 Natcheff N, Logofetov A, Tzaneva N. Hypothalmic control of plasma renin activity. *Pflugers Arch* 1977;371:279–83.

78 Jarechi M, Thoren PN, Donald DE. Release of renin by the carotid baroreflex in anaesthetised dogs. *Circ Res* 1978;42:614–9.

79 Thames MD, Jareski M, Donald DE. Neural control of renin secretion in anaesthetised dogs. *Circ Res* 1978;42:237–45.

80 Michelakis AN, McAllister RG. The effect of chronic adrenergic blockade on plasma renin activity in man. *J Clin Endocrinol Metab* 1972;34:386–94.

81 Bonelli J, Waldausl W, Magometchnigg D, Schwarzmeier J, Korn A, Hitzenberger G. Effect of exercise and of prolonged oral administration of propranolol on hemodynamic variables, plasma renin concentration, plasma aldosterone and cAMP. *Eur J Clin Invest* 1977;7:337–43.

82 Clamge DM, Sanford CS, Vander AJ, Mouw DR. Effects of psychosocial stimuli on plasma renin activity in rats. *Am J Physiol* 1976;231:1290–4.

83 Davalos M, Frega NS, Saker B, Leaf A. Effect of exogenous and endogenous angiotensin II in the isolated perfused rat kidney. *Am J Physiol* 1978;235:F605–10.

84 Watkins L Jr, Burton JA, Haber E, Cant JR, Smith FW, Barger AC. The renin-aldosterone system in congestive failure on conscious dogs. *J Clin Invest* 1976;57:1606–17.

85 Johnston CI, Davis JO, Robb CA, Mackenzie JW. Plasma renin in chronic experimental heart failure and during renal sodium "escape" from mineralocorticoids. *Circ Res* 1968;22:113–25.

86 Robinson FH Jr, Farr LE. Relation between clinical edema and the excretion of an anti diuretic substance in the urine. *Ann Intern Med* 1940;14:42–54.

87 Bercu BA, Rokaw SN, Massie E. Antidiuretic action of urine of patients in cardiac failure. *Circulation* 1950;2:409–13.

88 Yamane Y. Plasma ADH levels in patients with congestive failure. *Jpn Circ J* 1968;32:745–59.

89 Anderson RJ, Cadnapaphornchai P, Harbottle JA, McDonald KM, Schrier RW. Mechanism of effect of thoracic inferior vena cava constriction on renal water excretion. *J Clin Invest* 1974;**54**:1473–9.

90 Arnauld E, Czernichow P, Fumoux F, Vincent JD. The effects of hypotension and hypovolemia on the liberation of vasopressin during hemorrhage in the unanesthetized monkey. *Pflugers Archiv* 1977; 371:193–200.

91 Gilmore JP, Zucker IH. Failure of left atrial distention to alter renal function in the nonhuman primate. *Circ Res* 1978;**42**:267–70.

92 de Bold AJ. Heart atria granularity. Effects of changes in water electrolyte balance. *Proc Soc Exp Biol Med* 1979;**161**:508–11.

93 de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 1981;**28**:89–94.

94 Atlas SA, Kleinert HD, Camargo MJ. Purification, sequencing and synthesis of natriuretic and vasoactive rat atrial peptide. *Nature* 1984;**309**:717–9.

95 Maki M, Takayanagi R, Misono KS, Pandey KN, Tibbetts C, Inagami T. Structure of rat atrial natriuretic factor precursor deduced from cDNA sequence. *Nature* 1984;**309**:722–4.

96 Trippodo NC, Ghai RD, MacPhee AA, Cole FE. Atrial natriuretic factor: atrial conversion of high to low molecular weight forms. *Biochem Biophys Res Commun* 1984;**119**:282–8.

97 Dietz JR. Release of natriuretic factor from rat heart-lung preparations by atrial distension. *Am J Physiol* 1984;**247**:R1093–6.

98 Shanker Y, Sider RS, Ostafin EA, Grekin RJ. Plasma levels of immunoreactive atrial natriuretic factor in healthy subjects and in patients with oedema. *J Clin Invest* 1985;**76**:1684–7.

99 Briggs JP, Steipe B, Schubert G, Schnermann J. Micropuncture studies of the renal effects of atrial natriuretic substance. *Pflugers Arch* 1982;**395**: 271–6.

100 Grammer RT, Fukumi H, Inagami T, Misono KS. Rat atrial natriuretic factor. Purification and vasodilator activity. *Biochem Biophys Res Commun* 1983;**116**: 696–703.

101 Harris P. Evolution and the cardiac patient. *Cardiovasc Res* 1983;**17**:313–9,373–8,437–45.

102 Donald KW, Gloster J, Harris EA, Reeves J, Harris P. The production of lactic acid during exercise in normal subjects and in patients with rheumatic heart disease. *Am Heart J* 1961;**62**:494–510.

103 Petro JM, Hollander AP, Bouman LN. Instantaneous cardiac acceleration in man induced by a voluntary muscle contraction. *J Appl Physiol* 1970;**29**:794–8.

104 Alam M, Smirk FH. Observations in man upon a blood pressure raising reflex from the voluntary muscles. *J Physiol* 1937;**89**:372–83.

105 Alam M, Smirk FH. Observations in man on a pulse accelerating reflex from the voluntary muscles of the legs. *J Physiol (Lond)* 1938;**92**:167–77.

106 Tibes U, Hemmer B, Böning D. Heart rate and ventilation in relation to venous [K$^+$], osmolality, pH, P_{CO_2}, P_{O_2}, [orthophosphate], and [lactate] at transition from rest to exercise in athletes and non-athletes. *Eur J Applied Physiol* 1977;**36**:127–40.

107 Samet P, Fritts HW Jr, Fishman AP, Cournand A. The blood volume in heart disease. *Medicine (Baltimore)* 1957;**36**:211–35.

108 Dampney RAL, Goodchild AK, Robertson IG, Montgomery W. Role of ventrolateral medulla in vasomotor regulation: a correlative anatomical and physiological study. *Brain Res* 1982;**249**:223–35.

109 Gelsema AJ. A physiological review of mechanisms involved in the cardiovascular correlates of muscular activity. In: Grossman P, Janssen KHL, Vaitl D, eds. *Cardiorespiratory and cardiosomatic psychophysiology*. New York: Plenum Press, 1986:41–55.

110 Liu CT, Huggins RA, Hoff HE. Mechanisms of intra-arterial K$^+$-induced cardiovascular and respiratory responses. *Am J Physiol* 1969;**217**:969–73.

111 Coote JH, Hilton SM, Perez-Gonzalez JF. The reflex nature of the pressor response to muscular exercise. *J Physiol (Lond)* 1971;**215**:789–804.

112 McCloskey DI, Mitchell JH. Reflex cardiovascular and respiratory responses originating in exercising muscle. *J Physiol (Lond)* 1972;**224**:173–86.

113 Kalia M, Mei SS, Kao FF. Central projections from ergoreceptors (C fibers) in muscle involved in cardiopulmonary responses to static exercise. *Circ Res* 1981;**48**:48–62.

114 Sato A, Schmidt RF. Somatosympathetic reflexes: afferent fibers, central pathways, discharge characteristics. *Physiol Rev* 1973;**53**:916–47.

115 Schulz B, Lambertz M, Schulz G, Langhorst P. Reticular formation of the lower brainstem. A common system for cardiorespiratory and somatomotor functions: discharge patterns of neighboring neurons influenced by somotosensory afferents. *J Auton Nerv Syst* 1983;**9**:433–49.

116 Epstein FH, Post RS, McDowell M. Effects of an arteriovenous fistula on renal hemodynamics and electrolyte exertion. *J Clin Invest* 1953;**32**:233–41.

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The pathology of the early and late stages of primary pulmonary hypertension

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SUMMARY During the course of a case of primary pulmonary hypertension occurring in a 24 year old man lung tissue became available at heart-lung transplantation in 1986 and from a lung biopsy carried out in 1981. In 1986 the sections showed classic plexogenic pulmonary arteriopathy. In 1981 they revealed migration of myofibroblasts into the intima and lumen of pulmonary arteries and arterioles, the identification of the cells being confirmed by electron microscopy. During the five years that the pulmonary vascular pathology progressed to the formation of plexiform lesions there was an increase in the number of bronchiolar endocrine cells that were immunoreactive to bombesin and calcitonin.

This study demonstrates that the classic pathogenesis of primary plexogenic pulmonary arteriopathy originates years earlier as a migration of cells of muscular pedigree from the media into the intima of the pulmonary arteries and arterioles.

The histological features of fully developed plexogenic pulmonary arteriopathy, which forms the pathological basis for primary pulmonary hypertension, are well known. We have recently described them in detail together with the less familiar ultrastructural characteristics.[1] There is much less information on the histological and ultrastructural features of the early stages of the disease before the appearance of the plexiform lesions, fibrinoid necrosis, and "onion-skin proliferation" in pulmonary arteries. Yet this early stage is of great interest to the pathologist because familiarity with its features will enable him to diagnose with more confidence plexogenic pulmonary arteriopathy before the plexiform lesions develop. As the term implies, every case need not have plexiform lesions—only the potential to develop them. The early stage is also of prime interest to the clinician since analysis of the initial pathological lesions may suggest to him which treatment, if any, is likely to alleviate or even reverse the condition before it progresses to the fully developed disease for which heart-lung transplantation is the only treatment.

The difficulty has been that in most early cases of primary pulmonary hypertension the histopathologist has to assume without proof that the lesions he is describing will progress to classic plexogenic pulmonary arteriopathy. It is unusual to be able to study the pulmonary vascular lesions at an early stage in an individual case in which there is unequivocal progression of the lesions to the immediately recognisable disease and to have the opportunity to study lung tissue removed at heart-lung transplantation. For this reason we thought it was worth while to report the histological findings in such a case in which the observations were separated by a period of five years. The case is of added interest in demonstrating for the first time that primary plexogenic pulmonary arteriopathy may be associated with abnormal numbers of cells that are immunoreactive for certain peptides in the epithelium of the bronchial tree.

Case report

The patient was a paint sprayer. In 1980, at the age of 18 years, cardiomegaly was found at routine mass *x* ray. He had no symptoms at that time. A cardiac

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murmur had been noted in infancy but his parents had been advised that he would "grow out of it". Throughout childhood and adolescence he had been free from cardiac symptoms. On admission to hospital the pulse was regular at 80 beats/minute. The jugular venous pressure was normal and the systemic blood pressure 130/80 mm Hg. There was a slight prominence of the left chest. At the left sternal border there was an ejection click, a grade 1/6 ejection systolic murmur, fixed splitting of the second sound, and a grade 2/6 early diastolic murmur. The radiograph of the chest showed dilatation of the pulmonary trunk and its main branches (fig 1a). The electrocardiogram showed right ventricular hypertrophy. At cardiac catheterisation the pulmonary arterial pressure was 70/24 mm Hg. There was no evidence of a shunt. A pulmonary angiogram demonstrated a considerable enlargement of the pulmonary trunk and its major divisions. There was some reflux across the pulmonary valve. The right ventricle was enlarged but the left atrium and ventricle appeared normal. A lung scan showed some underperfusion of the middle and upper zones that was not thought to be suggestive of pulmonary embolisation. Respiratory function tests were normal. A diagnosis of primary pulmonary hypertension was made. He was treated with hydralazine. In 1981 a biopsy specimen of the lung was taken. In 1983 he complained of occasional pains in the chest and treatment was changed to nifedipine. At that point he became lost to follow up.

In November 1985 he was again admitted to the Leeds General Infirmary. He had had increasing dyspnoea on exertion for six months. More recently he had developed precordial pain on exertion and swelling of the ankles. On three occasions he had lost consciousness during exertion. He was taking 10 mg nifedipine three times a day together with diuretics. There was oedema of the legs. The jugular venous pressure was raised 5 cm with prominent "a" waves. The systemic arterial pressure was 90/70 mm Hg. The heart was enlarged with a prominent systolic outward movement of the entire precordium. A fourth sound was present, together with a loud second and an ejection click, grade 4/6 ejection systolic murmur, and grade 3/4 diastolic murmur at the left border of the sternum. The liver was palpable 5 cm below the costal margin. He was jaundiced. The chest radiograph showed enlargement of the heart and considerable dilatation of the pulmonary trunk and its primary and proximal branches (fig 1b). The electrocardiogram indicated severe right ventricular hypertrophy. Echocardiography confirmed dilatation of the right ventricle and right atrium.

He was assessed and accepted for cardiopulmonary transplantation at the National Heart Hospital and sent back to Leeds to await operation. Within two months, however, he developed severe generalised oedema and ascites with increasing renal and hepatic failure. A hepatic biopsy specimen

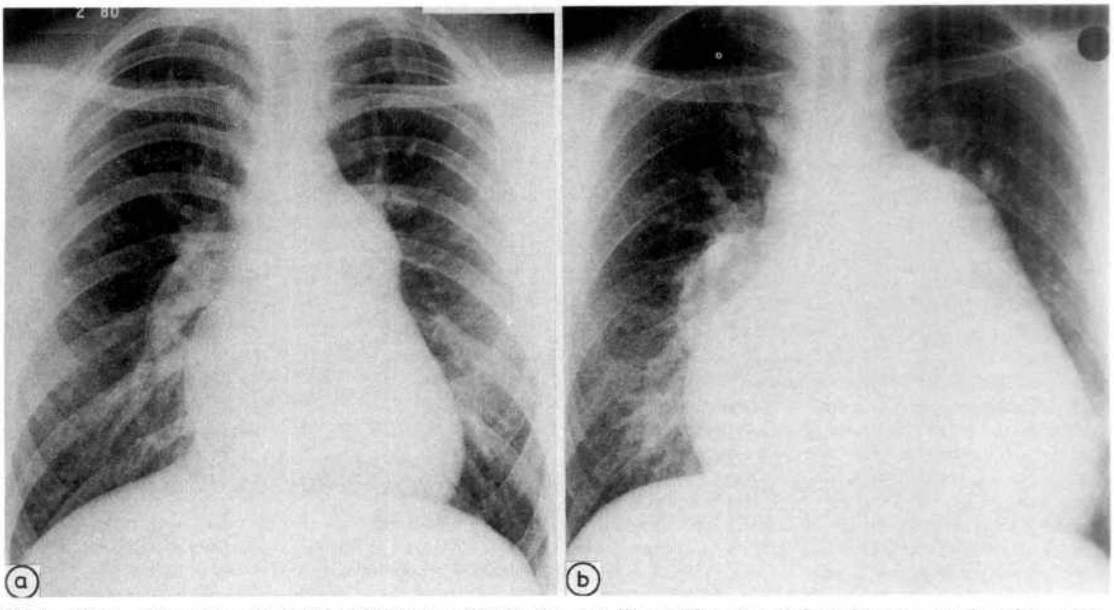

Fig 1 *Chest radiographs obtained in 1980 (a) and 1986 (b). (a) Shows dilatation of the pulmonary trunk and its main branches. The aortic arch appears small. The cardiothoracic ratio was 1:2. (b) The dilatation of the pulmonary trunk and its proximal branches has progressed and considerable cardiac enlargement has developed.*

showed evidence of severe venous congestion but no underlying chronic liver disease. Intensive treatment with albumin infusions and diuretics produced some amelioration before transplantation was attempted. He did not regain consciousness after the operation, although cardiopulmonary function was adequate.

Pulmonary vascular pathology in 1986

The histological features of the lung resected at heart-lung transplantation were typical of advanced plexogenic pulmonary arteriopathy. The elastic pulmonary arteries showed severe atherosclerosis. There was gross intimal proliferation of atherosclerotic tissue which had penetrated through the internal elastic lamina deep into the underlying media where it replaced the existing musculoelastic tissues. There was severe medial hypertrophy of the muscular pulmonary arteries; the total wall thickness was some 25% of the external diameter (fig 2). Sections stained with haematoxylin and eosin showed the compact media to be composed of circumferentially orientated smooth muscle cells with an inner layer of myofibroblasts whose nuclei were arranged radially (fig 2). Sections stained with an elastic van Gieson stain demonstrated the hypertrophied media delineated by inner and outer elastic laminae. This staining technique revealed that the inner zone of radially arranged myofibroblasts had formed a layer of musculoelastic tissue. This prominent layer of concentric-laminar musculoelastic tissue in the intima extended into many of the branches of the muscular pulmonary arteries where it considerably reduced the lumen (fig 3). In this layer the muscle cells were prominent and well defined and the elastic tissue was arranged as thick, well defined laminae (fig 3).

Plexiform lesions were much in evidence (fig 2). In sections stained by haematoxylin and eosin they appeared as dilated branches of muscular pulmonary arteries in which there had been a proliferation of cells, which we know from previous ultrastructural studies to be a mixture of myofibroblasts and primitive vasoformative reserve cells previously termed

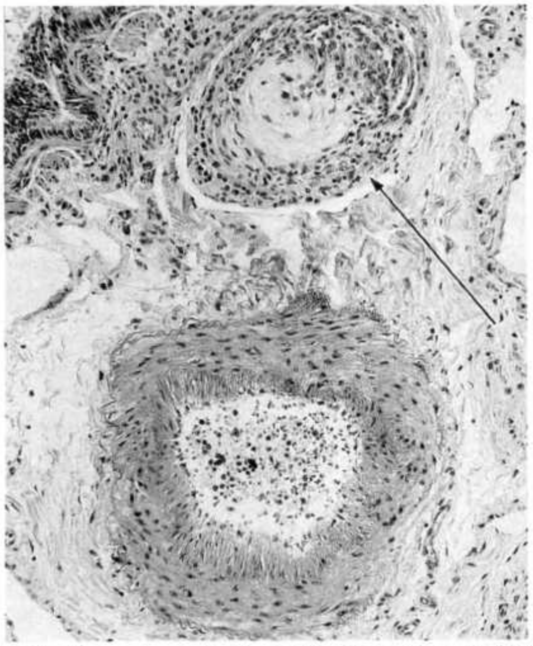

Fig 2 *Photomicrograph of a section of lung tissue obtained in 1986. In the lower half of the figure is a transverse section of a hypertrophied muscular pulmonary artery in which circumferentially oriented smooth muscle cells are tightly packed together. Internal to this is a zone where the nuclei of myofibroblasts are aligned radially. Including this layer, the wall thickness is about 25% of the diameter of the vessel. Above is a plexiform lesion (arrow) in which myofibroblasts and primitive vasoformative "fibrillary cells" have proliferated inside a dilated branch of the hypertrophied parent artery. (Haematoxylin and eosin; × 140.)*

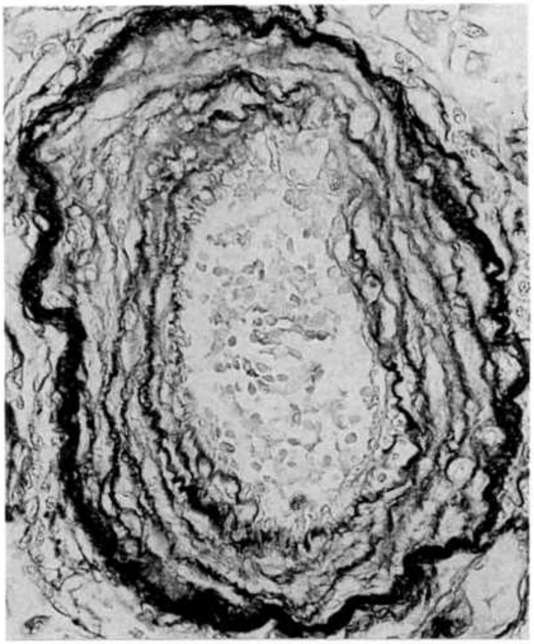

Fig 3 *Photomicrograph of a section of lung tissue obtained in 1986. Transverse section of dilated branch of muscular pulmonary artery showing a very thick outer limiting layer of elastic tissue and a prominent concentric-laminar layer of musculo-elastic tissue. Within this layer the elastic fibrils are thick and well defined. The muscle layers are prominent. (Elastic van Gieson; × 450.)*

"fibrillary cells.[2] In sections stained by the elastic van Gieson technique the limiting remains of the media of the dilated branch of the muscular pulmonary artery could be made out (fig 4). Some plexiform lesions arose as side-branches of the largest muscular pulmonary arteries which showed severe intimal fibroelastosis. Many of the small muscular pulmonary arteries showed concentric-laminar ("onion-skin") intimal proliferation (fig 5). A few showed subacute necrotising arteritis with replacement of lengths of media by fibrous tissue as part of a process of repair of necrotic media. There were small focal collections of siderophages in the alveolar spaces; these had probably resulted from haemorrhage from thin-walled branches of muscular pulmonary arteries.

Pulmonary vascular pathology in 1981

The histological features of the lung-biopsy specimen resected in 1981 differed in important respects from the picture of classic plexogenic pulmonary arteriopathy found in 1986 and described above. At that time the muscular pulmonary arteries already showed pronounced medial hypertrophy, the medial thickness approaching 15% of the external diameter of arteries which were around 270 µm in diameter (fig 6). The muscular pulmonary arteries had thick inner and outer elastic laminae which were in part crenated. Wispy elastic fibrils were seen in the substance of the media. In some of the larger muscular pulmonary arteries there were fasciculi of longitudinal smooth muscle in the outer media at its interface with adventitia; in others there were eccentric bundles of musculoelastic tissue in the intima. In other muscular pulmonary arteries there were crescentic areas of intimal elastic tissue (fig 6). Some of their branches were almost blocked by concentric-laminar intimal elastosis (fig 7) that resembled the changes seen in the lung five years later. In the lesions seen in 1981 the elastic fibrils were wispy and ill-defined (fig 7) compared with those seen in a similar situation five years later when the elastic fibrils were thicker, and well defined (fig 3). The parent elastic pulmonary arteries appeared normal with thick concentric elastic laminae embedded in the media of smooth muscle.

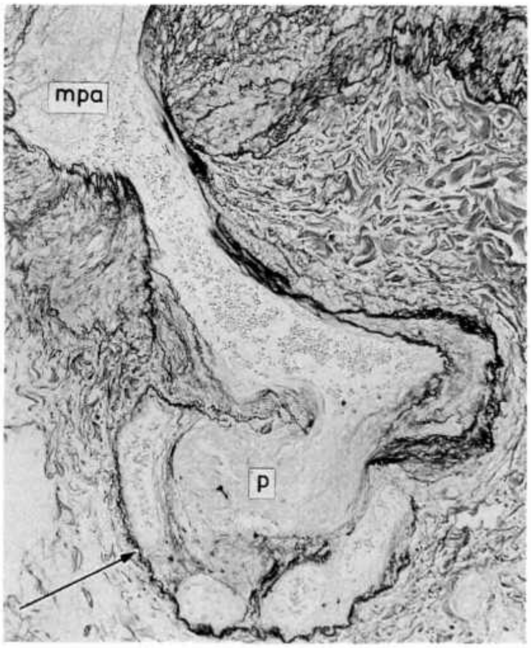

Fig 4 *Photomicrograph of a section of lung tissue obtained in 1986. Plexiform lesion (p) arising as a side-branch of a large muscular pulmonary artery (mpa) which itself shows prominent fibroelastic tissue. The remaining elastic tissue delineates the outer margin of the plexiform lesion (arrow). (Elastic van Gieson; × 135.)*

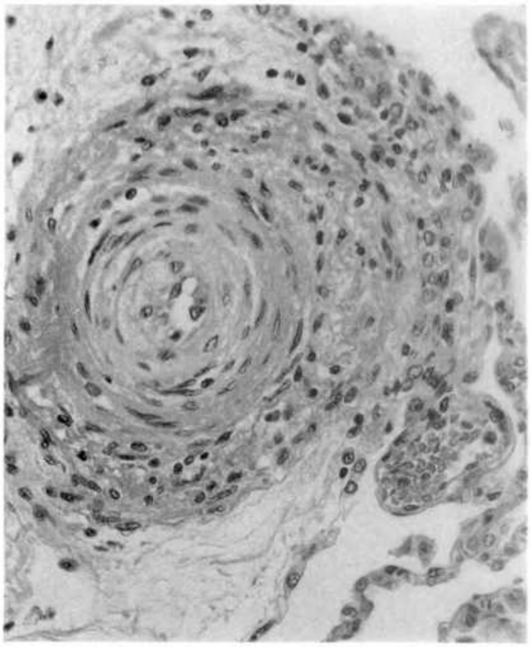

Fig 5 *Photomicrograph of a section of lung tissue obtained in 1986. Transverse section of a small, muscular pulmonary artery showing concentric-laminar ("onion-skin") proliferation of myofibroblasts. (Haematoxylin and eosin; × 350.)*

In the lung biopsy material resected in 1981 there was no intimal concentric-laminar ("onion-skin") proliferation, no fibrinoid necrosis, or necrotising arteritis, and, above all, no plexiform lesions. In the

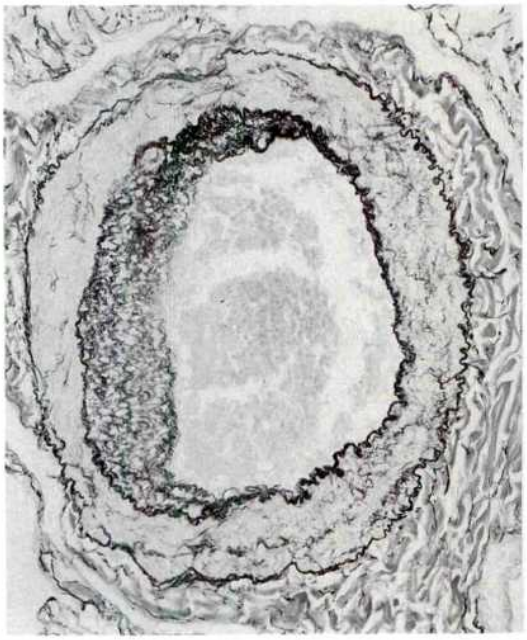

Fig 6 *Photomicrograph of a section of lung tissue obtained in 1981. Transverse section of muscular pulmonary artery showing medial hypertrophy; the thickness of the media was variable but averaged out at 15% of the external diameter of the vessel. There is a large crescentic mass of intimal fibroelastosis. (Elastic van Gieson; × 225.)*

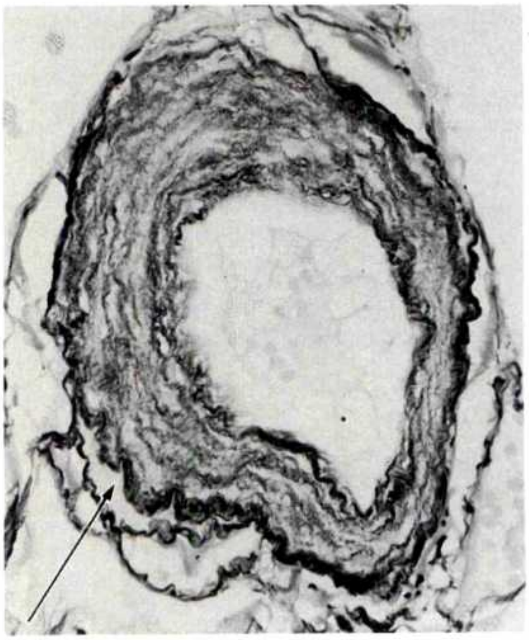

Fig 7 *Photomicrograph of a section of lung tissue obtained in 1981. Transverse section of thin-walled branch of muscular pulmonary artery whose wall is composed of a thick elastic lamina. The remains of the muscular media of the parent artery are indicated by an arrow. There is a thick layer of concentric-laminar intimal elastosis. (Elastic van Gieson; × 540.)*

earlier lung tissue, however, there were important lesions in the small muscular pulmonary arteries, pulmonary arterioles, and precapillaries. These took the form of a proliferation into the lumen of elongated cells with spindle-shaped nuclei that stained yellow with van Gieson's stain (fig 8). They had the cytological features of myofibroblasts. Loosely arranged in the lumen of the arterioles in a filigree pattern they maintained contact by many slender, elongated processes with the elastic lamina that made up the wall of the arteriole. In some instances there was migration of the myofibroblasts through the elastic wall of the pulmonary arteriole (fig 8). Both arterioles and precapillaries were packed with myofibroblasts. There was no intimal proliferation of any type in the pulmonary veins.

Electron microscopy

The lung biopsy specimen in 1981 was received fixed in formol saline, which is not ideal for electron microscopy. Nevertheless, small fragments of lung tissue were taken and processed for ultrastructural study. They were washed in buffer solution and fixed first in 3% glutaraldehyde and then in 1% osmium tetroxide. The tissue was then dehydrated in ethanol, embedded in Araldite, and stored for future use. Sections 1 μm in thickness were stained with toluidine blue and areas of tissue containing pulmonary blood vessels were selected for study. The blocks were then trimmed and fine sections were cut and then stained with uranyl acetate and lead citrate. The sections were studied with an AEI Corinth 500 electron microscope.

Muscular pulmonary arteries showed hypertrophy of the media, which was made up of numerous smooth muscle cells that were orientated circumferentially except for occasional longitudinally oriented groups adjacent to the adventitia. The muscle cells had elongated nuclei, often with a crenated outline, and a cytoplasm filled with myofilaments and containing cigar-shaped dense bodies, the so-called "focal condensations". The periphery of the smooth muscle cells bore numerous, dark attachment points interspersed with paler regions containing micropinocytotic vesicles. In some areas medial smooth muscle cells adjacent to the internal elastic lamina had adopted a radial ori-

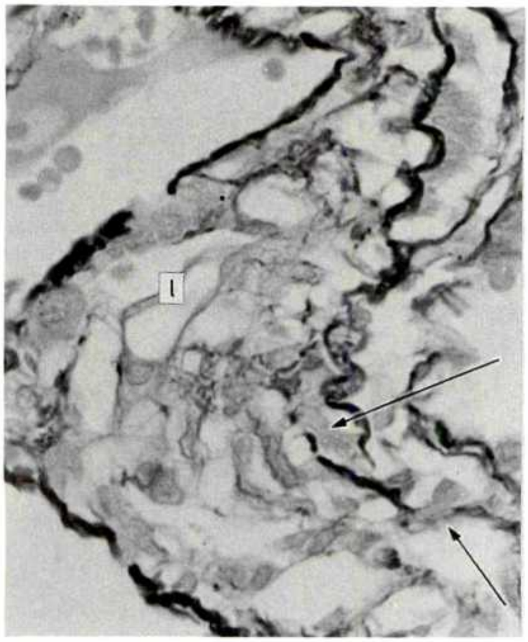

Fig 8 *Photomicrograph of a section of lung tissue obtained in 1981. Longitudinal section of pulmonary arteriole showing migration of myofibroblasts into the lumen (l). Sites where the cells are traversing elastic laminae are indicated by arrows. The cells have an irregular, elongated shape. (Elastic van Gieson; × 938.)*

entation as though migrating towards the intima (fig 9). In no instance were we able to demonstrate a muscle cell actually penetrating the elastic lamina, although this appearance was seen in the histopathological sections. Inside the inner lamina there were proliferating cells in the intima with ultrastructural features such as myofilaments and focal condensations that showed their muscular pedigree (fig 10). The intercellular spaces contained finely fibrillary ground substance, numerous collagen fibres (fig 9), and small deposits of immature elastin (fig 10). In view of their obviously secretory function we prefer to call the cells in the intima, "myofibroblasts". The fragmented internal elastic lamina was largely obscured by the profusion of collagen fibres and immature elastin.

Pulmonary arterioles showed the same intense proliferation of myofibroblasts in the intima but in these vessels the cells were much paler than their arterial counterparts and contained fewer myofilaments and focal condensations. In some myofibroblasts there was cytoplasmic vacuolation and disruption of mitochondria. This may have been an artefact caused by the initial slow formalin fixation. There was less intercellular ground substance and collagen in pulmonary arterioles than in muscular pulmonary arteries and there was very little elastin. The intimal myofibroblasts were separated from the endothelium by only a narrow basement membrane. Endothelial cells were compressed and displaced towards the lumen but were otherwise normal. They were readily identified because of the numerous Weibel-Palade bodies they contained. Myofibroblasts were also encountered in terminal arterioles which approached the size of precapillaries. In these small vessels they did not form a continuous intimal layer but rather a series of small pads projecting into the lumen. These cells were also pale and contained few myofilaments.

Pulmonary endocrine cells

Sections of lung were cut at 4 µm and labelled by the peroxidase-antiperoxidase method[3] with polyclonal primary antisera raised in rabbit to human neuron-specific enolase and calcitonin, bombesin, and leucine-enkephalin. The chromogen used was 3-amino-9-ethyl carbazole which gives a red-brown precipitate. We assessed the numbers of immunoreactive cells containing each of the peptides under study by counting their number and expressing it per square centimetre of tissue section as determined by planimetry, because the pulmonary tissue was collapsed. This method has been used successfully in previous studies.[4 5]

The cytology, histology, and distribution of endocrine cells in the pulmonary tissue from 1981 showed no abnormal features. Cells containing calcitonin and bombesin were scattered throughout the airways, occurring predominantly as solitary cells and occasionally as clusters. We did not find cells that were immunoreactive for leucine-enkephalin. All were immunoreactive for neuron-specific enolase, but none was argyrophilic irrespective of whether they contained calcitonin or bombesin. No cells containing calcitonin or bombesin were identified in the alveolar ducts or alveoli. In the three blocks of tissue examined (total sectional area $3{\cdot}65\,\text{cm}^2$) there were 3·3 cells per cm^2 that were immunoreactive for calcitonin and 9·0 cells per cm^2 that were immunoreactive for bombesin. The largest cluster seen contained five cells in one plane of section.

The appearance of the endocrine cells in the pulmonary tissue from 1986 was quite different. Cells containing calcitonin (fig 11) and bombesin (fig 12) were aggregated into clusters of variable size. In addition, the number of solitary endocrine cells containing these peptides was increased. Some of the clusters clearly consisted of aggregates of solitary cells and bore little resemblance to the normal neuroepithelial body. Two further features were notable. In some of the aggregates there was co-storage of bombesin and calcitonin. In others, the component cells were argyrophilic. As in the tissue from 1981, no cells that were immunoreactive for leucine-enkephalin were identified but all those containing bombesin or calcitonin or both were immunoreactive for neuron-specific enolase. No endocrine cells were identified in alveolar ducts or alveoli. In the four blocks of tissue examined, which made up a total sectional area of 10·85 cm^2, there were 21·2 cells per cm^2 that were immunoreactive for calcitonin and 50 cells per cm^2 that were immunoreactive for bombesin.

Discussion

There are many causes of a raised pulmonary arterial pressure and usually it is possible to demonstrate the basis of its development. There remains a small group of patients with clinically unexplained pulmonary hypertension. The pathological basis for pulmonary hypertension in these patients is usually plexogenic pulmonary arteriopathy, pulmonary veno-occlusive disease, or recurrent pulmonary thromboembolism.[1] A fourth pathological entity, the recently described invasive pulmonary capillary haemangiomatosis,[6-8] may need to be added to this list, although here the characteristic recurrent

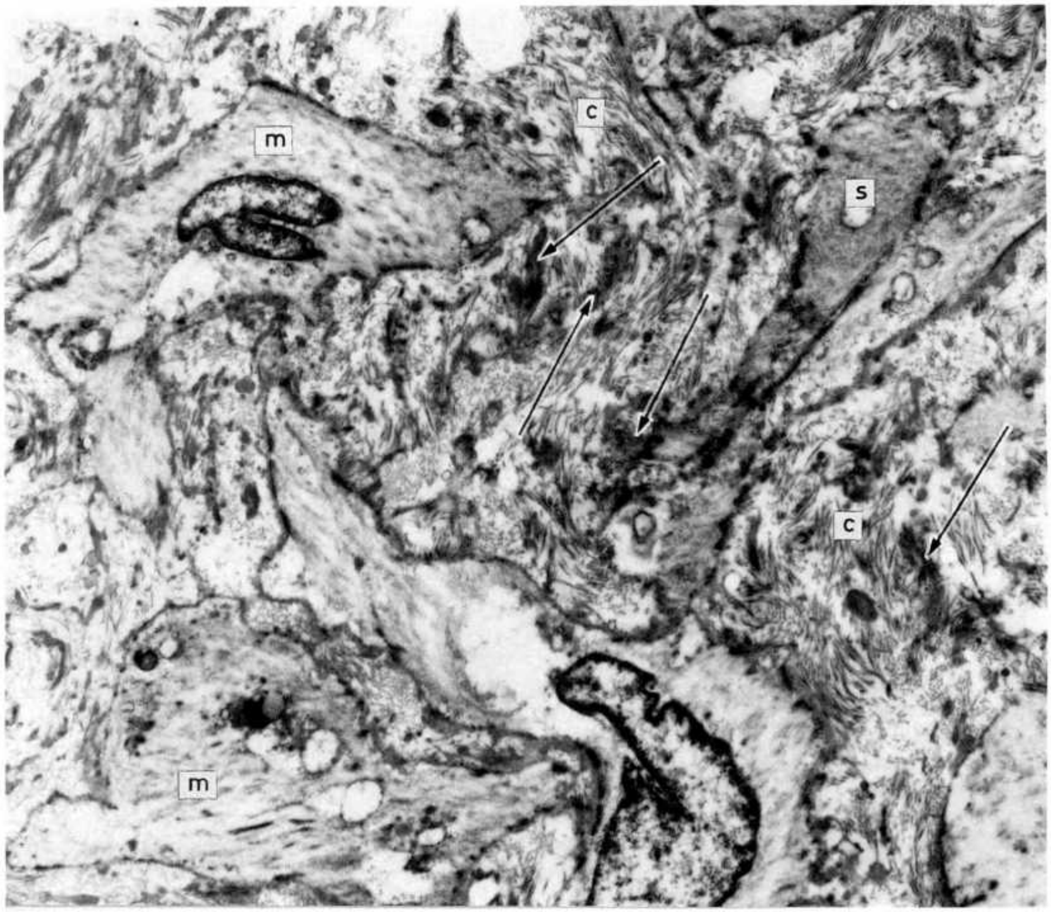

Fig 9 *Electron micrograph (tissue obtained in 1981) of part of the wall of a muscular pulmonary artery at the junction of media and intima. The internal elastic lamina is indistinct and consists of small, dark fragments of elastic tissue (arrowed) separated by an extensive network of collagen fibres (c). Smooth muscle cells (s) in the media are orientated at right angles to the lamina and extend into it. The intima contains myofibroblasts (m), which are similar to smooth muscle, and sparsely distributed collagen fibres. (× 7000.)*

haemoptysis may allow clinical diagnosis. Commonly, however, clinical examination and investigation will not distinguish one condition from the other and an open lung biopsy is needed for precise diagnosis.

Plexogenic pulmonary arteriopathy, a term designated by a Working Party of the World Health Organisation[9] is not specific to primary pulmonary hypertension but also occurs in cases of pre- and post- tricuspid congenital cardiac shunt such as atrial and ventricular septal defect,[1] and of severe pulmonary hypertension complicating cirrhosis of the liver or portal vein thrombosis.[10] The feature which distinguishes this pathological entity in primary pulmonary hypertension is that it occurs on its own as primary plexogenic pulmonary arteriopathy.

The words of the designation of the disease were carefully chosen. Each case has the potential for forming plexiform lesions but they may not be present in any individual case. They take time to develop. The plexiform lesion is a dilated branch of a muscular pulmonary artery in which a plexiform mass of narrow vascular channels and cells forms.[1] The proliferation appears to be a response to fibrin and fibrinoid material derived from the media of the parent muscular pulmonary artery.[11] Our own electron microscopical studies[2] have shown that the vascular channels are not true capillaries since they are

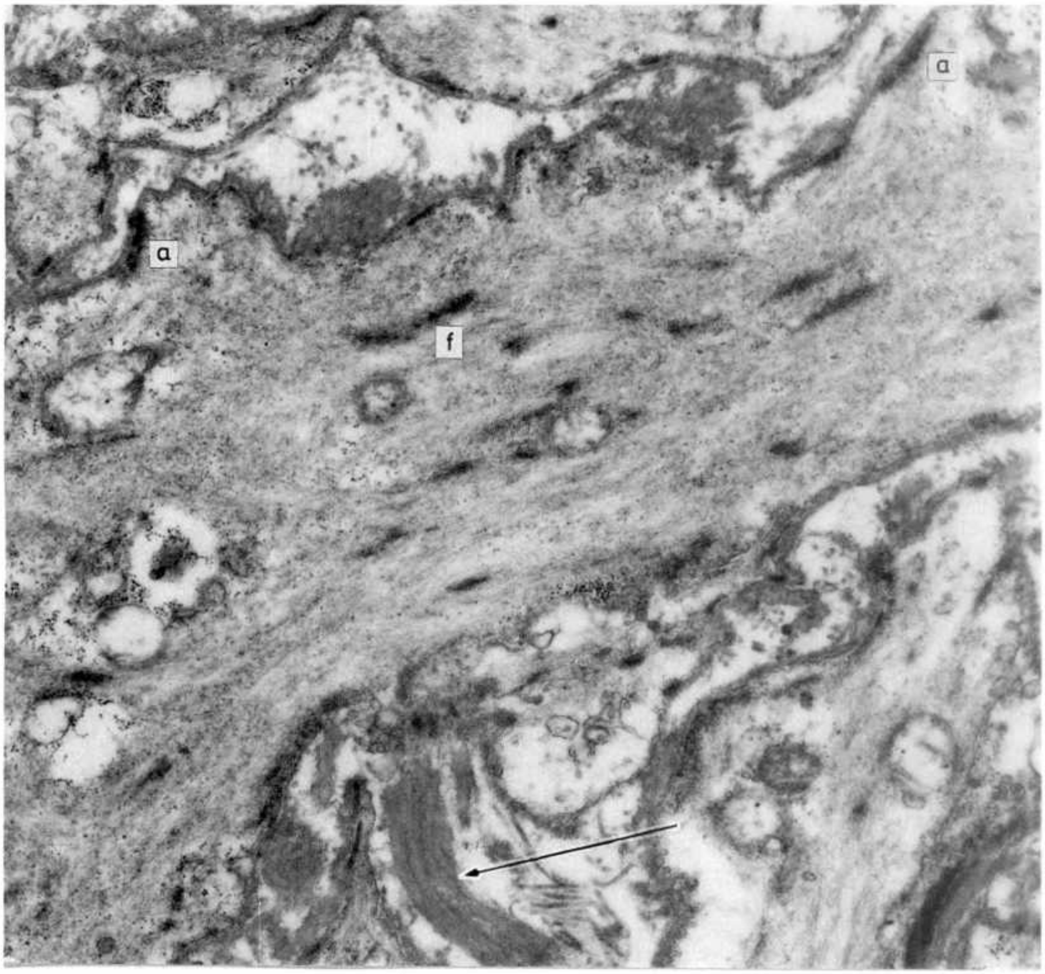

Fig 10 *Electron micrograph (tissue obtained in 1981) showing detail of a myofibroblast from an area of intimal elastosis in a muscular pulmonary artery. The cell contains numerous myofilaments, focal condensations (f), and peripheral attachment points (a). The intercellular space contains collagen fibrils and immature elastin (arrow). (× 17 500.)*

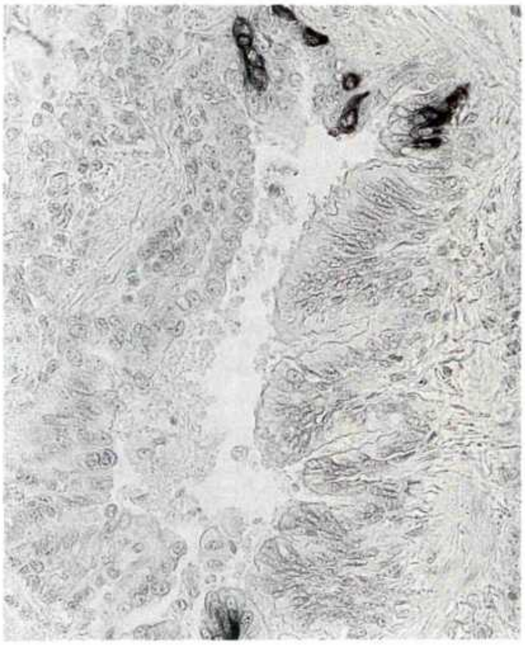

Fig 11 *Photomicrograph of a section of lung tissue obtained in 1986. Transverse section of small bronchiole showing cells immunoreactive for calcitonin in the bronchiolar mucosa. (Peroxidase-antiperoxidase; × 350.)*

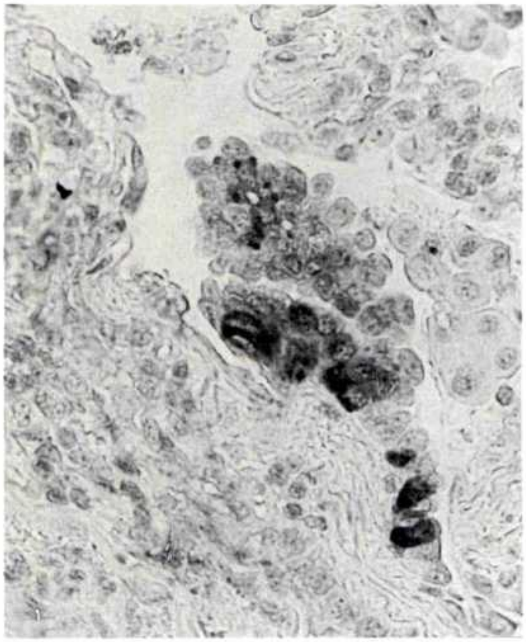

Fig 12 *Photomicrograph of a section of lung tissue obtained in 1986 showing a group of cells lining a small bronchiole that are immunoreactive for bombesin. (Peroxidase-antiperoxidase; × 562.)*

lined not by endothelial cells but by primitive vasoformative cells which we have called "fibrillary cells". The cytoplasm of these cells contains numerous microfilaments of uniform thickness arranged in whorls.[2] Between the vascular channels is a matrix of acid proteoglycans in which myofibroblasts and fibrillary cells are embedded. One associated histological lesion is concentric-laminar proliferation of cells ("onion-skin proliferation") in muscular pulmonary arteries or their branches; the cells which proliferate have been shown to be myofibroblasts.[2] Another is fibrinoid necrosis of the media of the parent artery in which fibrin and related substances may be released into dilated branches and stimulate the formation of plexiform lesions; the fibrinoid necrosis will also attract neutrophil polymorphs and thus give the picture of necrotising arteritis. When this characteristic triad of histological lesions occurs together in an advanced stage of plexogenic pulmonary arteriopathy the diagnosis is easy and straightforward.

The features of the early stages of proven plexogenic pulmonary arteriopathy are far less familiar and so the findings in the present case are of special interest. In this young man severe pulmonary vascular disease was already established five years before plexiform lesions were found in lung tissue resected at heart-lung transplantation, and one year later cardiomegaly was noted at mass *x* ray when the patient was free from symptoms. The initial vascular lesions included prominent medial hypertrophy indicative of a considerable increase in pulmonary arterial pressure and resistance as early as 1981 and this is consistent with the haemodynamic findings at that time. The second important component of the disease process at that time was a migration of cells from the media of muscular pulmonary arteries into the intima of the vessels and their branches. Electron microscopy demonstrated that these cells were myofibroblasts; so the striking proliferations of intimal elastosis and musculoelastosis in the pulmonary arteries (fig 6) and their branches (fig 7) were the result of formation of connective tissues of various types by cells of a *muscular* pedigree. The migration, proliferation, and secretory activity of these cells appeared to persist for years since the intimal muscularity and elastosis was still present in the lung tissue resected in 1986, albeit with certain changes such as the thickening and sharper modelling of the elastic fibres.

Myofibroblasts also migrated through deficiencies in the inner elastic lamina of the pulmonary arterioles, leading to occlusion of the lumen. Such appearances indicate that the early stage of plexogenic pulmonary arteriopathy is characterised by a hyperplasia of cells of muscular pedigree. Primary pulmonary hypertension is traditionally described as a vasospastic form of pulmonary vascular disease and the later stages of its pathology with fibrinoid necrosis are certainly consistent with that view. However, the earliest stages appear to be an active migration of muscle cells and this seems to have implications for treatment of the early stages of the disease because it is difficult to see how the administration of pulmonary vasodilators could influence this migration of muscle-derived cells to block the vascular lumen.

The stimulus for the migration of the myofibroblasts is obscure but in the present case there was evidence of increased immunoreactivity in the bronchiolar epithelial cells for both calcitonin and bombesin. Pulmonary endocrine cells containing these regulatory peptides were present in normal numbers in the lung tissue from 1981 but had increased by 1986. The content of bombesin in particular was abnormally high. It is traditional in defining primary pulmonary hypertension to state that the lung per se beyond the pulmonary vasculature is normal. The findings in the present case make it clear that this is not true. In this case there was unequivocal evidence of increased immunoreactivity for calcitonin and, especially, bombesin. At present it is difficult to see how increased secretions of regulatory peptides in the bronchial tree could induce proliferation and migration of the myofibroblasts in the pulmonary arteries. It seems that the stimulus for growth of the muscle cells would be more likely to originate in the closely adjacent endothelial cells. This aspect of the pathology of plexogenic pulmonary arteriopathy clearly requires further investigation.

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References

1 Harris P, Heath D. *The human pulmonary circulation. Its form and function in health and disease.* 3rd ed. Edinburgh: Churchill Livingstone, 1986.

2 Smith P, Heath D. Electron microscopy of the plexiform lesion. *Thorax* 1979;34:177–86.

3 Sternberger LA. The unlabelled antibody peroxidase-antiperoxidase (PAP) method. In: Sternberger LA, ed. *Immunocytochemistry.* New York: John Wiley, 1979:104–69.

4 Taylor W. Pulmonary argyrophil cells at high altitude. *J Pathol* 1977;122:137–44.

5 Sissons MCJ, Gosney JR. Pulmonary endocrine cells immunoreactive for calcitonin in the lungs of fetal and neonatal rats. *Thorax* 1985;40:862–5.

6 Wagenvoort CA, Beetstra A, Spijker J. Capillary haemangiomatosis of the lungs. *Histopathology* 1978;2:401–6.

7 Whittaker JS, Pickering CAC, Heath D, Smith P. Pulmonary capillary haemangiomatosis. *Diagnostic Histopathology* 1983;6:77–84.

8 Heath D, Reid R. Invasive pulmonary haemangiomatosis. *Br J Dis Chest* 1985;79:284–94.

9 Hatano S, Strasser T, eds. *Primary pulmonary hypertension. Report on a WHO meeting, Geneva, October 1973.* Geneva: World Health Organisation, 1975.

10 Saunders JB, Constable TJ, Heath D, Smith P, Paton A. Pulmonary hypertension complicating portal vein thrombosis. *Thorax* 1978;34:281–3.

11 Wagenvoort CA. The morphology of certain vascular lesions in pulmonary hypertension. *J Pathol Bacteriol* 1959;78:503–11.

Br Heart J 1987;**58**:214–7

Ventricular septal defect after myocardial infarction: assessment by cross sectional echocardiography with pulsed wave Doppler scanning

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SUMMARY Eight patients who developed a ventricular septal defect after myocardial infarction were assessed by cross sectional echocardiography and pulsed wave Doppler scanning. Cross sectional echocardiography visualised the defect in four patients and gave an accurate assessment of global and regional left ventricular function in all eight. In all patients pulsed wave Doppler scanning detected turbulent flow at the apex of the right ventricle or adjacent to a wall motion abnormality affecting the interventricular septum. Pulsed wave Doppler detected coexisting mitral regurgitation in one patient and tricuspid regurgitation in another two. In all patients a left to right shunt was confirmed by oximetry and the location of the defect was identified by angiography or at operation or necropsy.

Cross sectional echocardiography in combination with pulsed wave Doppler scanning is useful in the rapid bedside evaluation of patients with ventricular septal defect after myocardial infarction.

Rupture of the interventricular septum is a life threatening complication that occurs in 0·5–1·0% of patients with acute myocardial infarction. Typically, a patient presents with haemodynamic deterioration and the development of a pansystolic murmur, usually within a week of acute myocardial infarction. Early and accurate diagnosis, and in particular distinction from acute mitral regurgitation, is essential because an appropriate operation may be life saving. The diagnosis of septal rupture has usually been confirmed by demonstrating a left to right shunt with oximetry at Swan-Ganz catheterisation and by contrast ventriculography, but a reliable non-invasive bedside technique would be preferable. Cross sectional echocardiography can demonstrate the actual defect and the reliability of this technique may be enhanced by the injection of agitated saline into a peripheral or central vein to act as an echocardiographic contrast medium.[1] Recently, pulsed wave Doppler scanning has been used to demonstrate abnormal intracardiac flow adjacent to the suspected defect.[2–4] We report our experience with combined cross sectional echocardiography and pulsed wave Doppler scanning in eight consecutive cases of postinfarction ventricular septal rupture.

Patients and methods

PATIENTS

Since March 1985 all patients in our coronary care unit or referred from outside hospitals with suspected ventricular septal rupture after myocardial infarction have had cross sectional echocardiographic studies with pulsed wave Doppler scanning. During this time we have studied eight patients with postinfarction ventricular septal defect confirmed by angiography or at operation or necropsy.

The table summarises the clinical details of the eight patients. Three patients had inferior and five had anterior myocardial infarction and all developed a pansystolic murmur. Patient 5 developed a 2/6 pansystolic murmur ten days after anterior myocardial infarction and was thought both clinically and on the basis of cross sectional echocardiography with pulsed wave Doppler scanning to have devel-

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oped mild mitral regurgitation. She was discharged but six days later she was readmitted with pulmonary oedema and a 4/6 pansystolic murmur. A ventricular septal defect and mitral regurgitation were found. Patient 8 first presented with dyspnoea but gave a history typical of myocardial infarction occurring two weeks previously.

ECHOCARDIOGRAPHIC EXAMINATION

Cross sectional echocardiography with pulsed wave Doppler scanning was performed with a Hewlett-Packard model No 77020A phased array echocardiograph and integral pulsed Doppler system. Seven of the eight patients were studied within 24 hours of the development of the murmur and in six cases this was before oximetry or contrast ventriculography. We attempted to record parasternal long and short axis views and apical two and four chamber views. In all views we attempted to visualise the ventricular septal defect directly, particularly in the four chamber and parasternal short axis views. The transducer was swept through an arc to image as much of the septal anatomy as possible. Global and regional left ventricular function was assessed from the cross sectional echocardiographic images. For pulsed wave Doppler analysis the sample volume was placed to interrogate the apex and body of both ventricles and also the atria to determine whether mitral or tricuspid regurgitation could be detected.

In all cases ventricular septal rupture was confirmed by oximetry or left ventricular angiography in the 45° left anterior oblique projection or both. Anatomical confirmation was obtained in seven cases at operation or necropsy.

Results

CROSS SECTIONAL ECHOCARDIOGRAPHY

Wall motion abnormalities—Assessment of regional left ventricular wall motion abnormalities and global function by cross sectional echocardiography accorded with abnormalities demonstrated at angiography. The left ventricular apex was affected in all cases whether the electrocardiographic site of infarction was inferior or anterior.

Direct visualisation of the defect—In patients 1, 2, 3, and 7 the defect could be seen clearly by cross sectional echocardiography in the apical four chamber and parasternal short axis views over the left ventricular apex. In one case (patient 3) the defect was shown to follow a serpentine course through the interventricular septum as the septum was imaged from apex to base, a finding that was confirmed at necropsy. In the remaining four cases (patients 4, 5, 6, and 8) a defect in the septum could not be visualised clearly but the septum appeared thin and hypo-

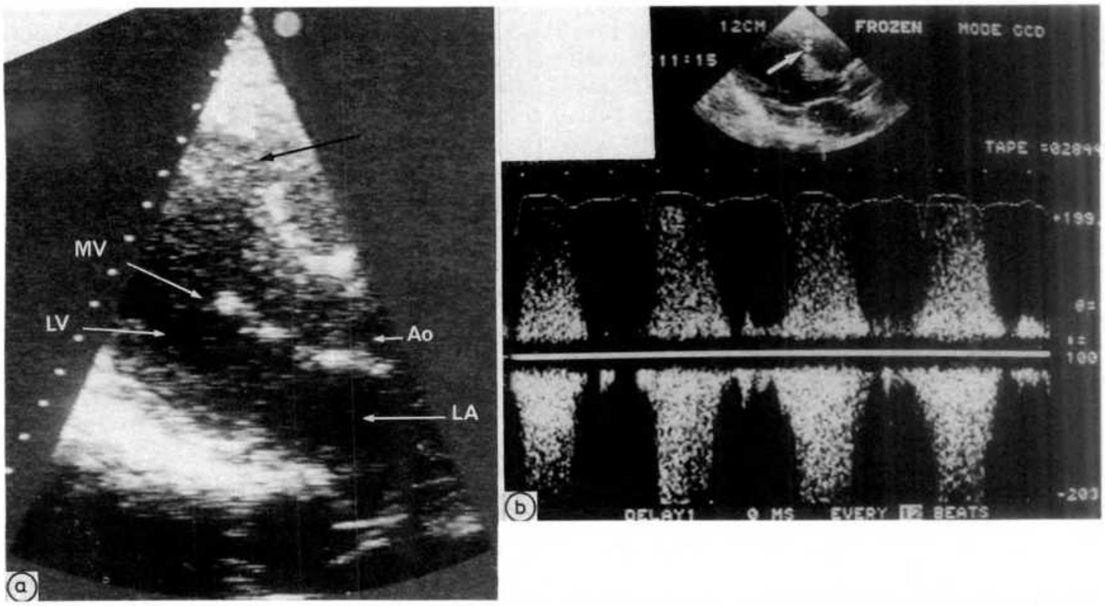

Fig *Cross sectional echocardiogram (a) in the parasternal long axis view showing a probable defect in the interventricular septum (black arrow). (b) A similar view in another patient with the pulsed wave Doppler sample volume adjacent to the ventricular septal defect (arrow). The Doppler signal shows turbulent flow with aliasing. LV, left ventricle; LA, left atrium; Ao, aortic root; MV, mitral valve.*

Table *Clinical characteristics and outcome of eight patients with ventricular septal rupture after myocardial infarction*

			Days after MI:			*NYHA class:*		
Patient	*Age and sex*	*ECG site of MI*	*To appearance of murmur*	*To operation*	*Auscultatory findings*	*At echo*	*At operation*	*Outcome*
1	69 F	Inferior	4	4	PSM 3/6	IV	IV	Repair + CABG, perioperative death
2	77 M	Anterior	4	9	PSM 3/6	II	IV	Repair + CABG
3	74 M	Inferior	6	None	PSM 3/6	IV	—	Death (cardiogenic shock)
4	69 M	Anterior	6	None	PSM 4/6	IV	—	Death (ventricular fibrillation)
5*	70 F	Anterior	10		PSM 2/6	II	—	Repair MVR + AVR, perioperative death
			20	22	PSM 4/6	IV	IV	
6	73 F	Anterior	2	13	PSM 4/6	II	II	Repair
7	65 M	Anterior	3	3	PSM 3/6	II	II	Repair
8	71 M	Inferior	Presented at 14 days	60	PSM 3/6	II	II	Repair + CABG

*Patient 5 had two examinations (see text).
MI, myocardial infarction; PSM, pansystolic murmur; NYHA, New York Heart Association; MVR, mitral valve replacement; AVR, aortic valve replacement; CABG, coronary artery bypass graft.

kinetic in the segment where the defect was demonstrated at angiography.

PULSED WAVE DOPPLER SCANNING

In patients 1, 2, 3, and 7 when the sample volume was placed adjacent to the septal defect and within the right ventricle a harsh Doppler audio signal was recorded in systole. Spectral analysis of the signal demonstrated multiple frequencies and aliasing of the signal, indicating turbulent and high velocity flow (fig). In two cases these signals could be detected with the sample volume located within the ventricular septal defect seen on cross sectional echocardiography. In patients 4, 5, 6, and 8 a similar Doppler signal was identified adjacent to the thin and akinetic segment of the interventricular septum (fig). In all cases the turbulent Doppler signal was clearly distinguishable from the normal laminar and biphasic flow pattern at the level of the tricuspid valve. Patients 2 and 6 had clinical evidence of tricuspid regurgitation and turbulent flow was detected within the right atrium by Doppler. Patient 5 had two studies: the first at 10 days demonstrated mitral regurgitation and the second, when there was a sudden clinical deterioration at 20 days, demonstrated both mitral regurgitation and a ventricular septal defect (table).

INVASIVE STUDIES

All eight patients had a left to right shunt confirmed by oximetry. Seven patients underwent contrast ventriculography which demonstrated the site of the defect. Of these, four had three vessel disease on coronary angiography and in all seven the artery supplying the territory of the myocardial infarction was occluded.

PATHOLOGICAL EXAMINATION

Six patients underwent surgical repair; four survived and two died perioperatively from pump failure. Patient 5 underwent repair of the ventricular septal defect and mitral valve replacement. Because the aortic valve was inadvertently damaged at operation this too was replaced (table). Two died within 48 hours of diagnosis, one suddenly from ventricular fibrillation and one in cardiogenic shock. The patient in cardiogenic shock (case 3) was considered to be inoperable on the basis of the cross sectional echocardiographic assessment of left ventricular function; angiography was not performed and at necropsy there was evidence of old anterior an recent inferoapical myocardial infarction with a s pentine defect through the basal and apical segments of the ventricular septum.

Discussion

We have shown that cross sectional echocardiography with pulsed wave Doppler scanning can demonstrate the presence of ventricular septal rupture after myocardial infarction, confirming the previous reports of Miyatake *et al*[2] and Cheesman *et al.*[4] In four of our eight patients the defect was visualised by cross sectional echocardiography. There was good agreement in the assessment of regional and global left ventricular function between cross sectional echocardiography and contrast ventriculography.

On initial study one patient (patient 5) was thought to have only mitral regurgitation. At a later study a ventricular septal defect had developed. It is possible that a ventricular septal defect was present at the time of the first study, but the patient's rapid deterioration and new clinical and Doppler echocardiographic findings strongly suggest that septal rupture occurred after the first examination.

We believe that cross sectional echocardiography with pulsed wave Doppler scanning can provide diagnostic confirmation and important information about global and regional left ventricular function at the bedside in patients with a suspected ventricular septal defect after myocardial infarction. This technique may reduce the necessity for full angiographic assessment of such patients, especially when poor left ventricular function excludes surgical intervention. It is also possible that operation could be considered without angiography or after coronary angiography alone.

References

1 Drobac M, Gilbert B, Howard R, Baigrie R, Rakowski H. Ventricular septal defect after myocardial infarction: diagnosis by two-dimensional contrast echocardiography. *Circulation* 1983;**67**:335–41.

2 Miyatake K, Okamoto M, Kinoshita N, *et al.* Doppler echocardiographic features of ventricular septal rupture in myocardial infarction. *J Am Coll Cardiol* 1985;**5**:182–7.

3 Eisenberg PR, Barzilai B, Perez JE. Non invasive detection by Doppler echocardiography of combined ventricular septal rupture and mitral regurgitation in acute myocardial infarction. *J Am Coll Cardiol* 1984;**4**:617–20.

4 Cheesman MG, John R, Murray N, Thomas J, Redding VJ. Pulsed Doppler ultrasound in the diagnosis of post-infarction ventricular septal defect [Abstract]. *Br Heart J* 1987;**57**:563.

Br Heart J 1987;58:218–24

Left ventricular function and oesophageal function in patients with angina pectoris and normal coronary angiograms

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SUMMARY Left ventricular function and oesophageal function (including oesophageal manometry and pH monitoring) were investigated and a psychiatric assessment carried out in 63 patients with angina pectoris and normal coronary angiograms. Twenty two (35%) patients had regional abnormalities of left ventricular wall motion (group A). Thirty six (57%) patients had an oesophageal abnormality (group B); 19 patients had gastro-oesophageal reflux and abnormal oesophageal motility, five had gastro-oesophageal reflux alone, and 12 had abnormal oesophageal motility alone. Only four had regional abnormalities of the left ventricular wall and abnormal oesophageal function. In nine (14%) patients left ventricular and oesophageal function were normal (group C). Psychiatric morbidity was significantly less common in group A than in groups B and C and was similar in group B and group C.

A definite abnormality of left ventricular function, oesophageal function, or psychiatric morbidity is present in a high proportion of patients with angina pectoris and normal coronary angiograms and in some instances this may lead to specific treatment. If quantitative assessment of left ventricular function is normal, oesophageal investigations should be performed. Endoscopy of the upper gastrointestinal tract may demonstrate oesophageal disease, but, if findings are normal, oesophageal manometry and ambulatory oesophageal pH monitoring (including during treadmill exercise testing) should be carried out.

Between 10% and 30% of patients referred for coronary angiography because of chest pain are found to have either normal coronary arteries or only minor narrowing of the coronary lumen.[1 2] It has been suggested that many of these patients have a non-cardiac cause for their chest pain, including oesophageal[3 4] and psychosomatic abnormalities.[5] In 1974, Richardson *et al* reported seven patients in whom endomyocardial biopsy specimens showed features of congestive cardiomyopathy.[6] We assessed left ventricular regional wall motion in 201 patients with angina pectoris and normal coronary angiograms and found that 35% had left ventricular systolic dysfunction.[7] Oesophageal function and left ventricular function, however, have not previously been investigated in the same group of patients.

This prospective study was carried out on a series of patients presenting with typical angina pectoris who had completely normal coronary angiograms. Left ventricular function and oesophageal function, including oesophageal manometry and 24 hour oesophageal pH monitoring, were investigated. The patients were also assessed for evidence of psychiatric disorders.

Patients and methods

PATIENTS

We studied 63 consecutive patients (40 women and 23 men aged 30–68 (mean 47) years) with suspected coronary heart disease who had been referred to the

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Regional Cardiac Unit, Wythenshawe Hospital, between January 1985 and June 1986 but in whom coronary angiography was normal. All patients complained of recurrent exertional chest pain which was typical of angina pectoris in its site, character, and radiation.[8] Their selective coronary angiograms, which had been performed in multiple views, were reviewed by three experienced observers and confirmed to be completely normal. Unlike many previous studies, we did not include patients with irregularities, even minor ones, on the coronary arteriogram. None of the patients had previously undergone any investigations of the gastrointestinal system.

LEFT VENTRICULAR FUNCTION

The left ventricular angiograms of all patients in this study showed satisfactory opacification of the chamber and the silhouettes could be traced. Only sinus beats that did not follow premature ventricular contractions were analysed. Three of the original 66 patients were excluded because their angiograms were not suitable for analysis. The left ventricular end systolic and end diastolic volumes and ejection fraction were calculated by the single plane area-length method after correction for magnification.[9] Left ventricular regional wall motion was measured by the technique described by Leighton *et al.*[10] The percentage of systolic shortening in seven hemiaxes (H_{1-7}) was calculated as previously described.[7] A hypokinetic segment was defined as a hemiaxis where the percentage of systolic motion was <2 SD from the normal mean.[10]

OESOPHAGEAL MANOMETRY

We examined all patients by fibreoptic upper gastrointestinal endoscopy with oesophageal biopsy before the oesophageal motility study. Oesophageal manometry was performed on a different occasion with an Arndorfer hydraulic capillary infusion system linked to a Lectromed multichannel pen recorder. All medication was discontinued 48 hours before a standard oesophageal manometric study.[11 12] We measured the pressure of the lower oesophageal sphincter and the peristaltic activity of the oesophageal body in response to 10 "wet swallows" (5 cm^3 water bolus). Sixty one of the 63 patients were then given 80 $\mu g/kg$ of edrophonium chloride intravenously[13 14] and the manometric response was recorded, together with any symptoms experienced by the patients.

The recordings were analysed blindly and interpreted according to previously reported normal values.[11 12 15 16] Oesophageal manometric abnormalities included hypertensive lower oesophageal sphincter ($\geqslant 30$ mm Hg), "nutcracker" oesophagus (mean amplitude in distal oesophagus $\geqslant 120$ mm Hg or maximum amplitude >200 mm Hg or both), prolonged contractions (mean duration $\geqslant 6$ seconds), repetitive contractions (at least three peaks), simultaneous contractions (non-peristaltic), and manometric abnormalities associated with usual chest pain after intravenous edrophonium (positive edrophonium challenge).

OESOPHAGEAL PH MONITORING

The first 11 patients were referred for endoscopy and oesophageal manometry. Concern about possible undiagnosed gastro-oesophageal reflux prompted 24 hour ambulatory intra-oesophageal pH monitoring in the next 52 patients.[17] All medication was discontinued 48 hours before and for the duration of this investigation. Patients were given a diary card to record the times of any symptoms and of eating, drinking, going to bed, and getting up. They activated an event marker at these times. During oesophageal pH monitoring the patients underwent symptom limited treadmill exercise testing by the standard Bruce protocol to determine whether exertional gastro-oesophageal reflux (pH <4) occurred.

The oesophageal pH record was analysed blindly, and a "score" was calculated as described by Johnson and DeMeester.[18] This was derived by use of six components from the 24 hour oesophageal pH record, and a score greater than 21·3 was considered to be abnormal.[18]

PSYCHIATRIC ASSESSMENT

All patients were assessed by an experienced psychiatrist who did not know the results of cardiac catheterisation (apart from the presence of normal coronary angiograms) or the oesophageal investigations. The patients underwent a standardised psychiatric interview, including the Clinical Interview Schedule.[19] The details of the psychiatric assessment will be published elsewhere, but for the purpose of this study patients were designated broadly as having a normal or abnormal psychiatric state.[5]

STATISTICAL ANALYSIS

We examined group differences by a one-way analysis of variance and compared proportions by the χ^2 test.

Results

In 41 (65%) patients regional motion of the left ventricular wall was normal. The remaining 22 (35%) patients had a total of 50 hypokinetic segments (group A): 10 had one hypokinetic segment, three

Table 1 *Oesophageal manometric abnormalities in 31 patients with angina pectoris and normal coronary angiograms*

Manometric abnormality	*No of patients*	*Comment*
Repetitive contractions	21*	—
Prolonged duration of contractions	19	18 had repetitive contractions, 1* had no other abnormality
Simultaneous contractions	10	7 had repetitive contractions, 3* had no other abnormality
Nutcracker oesophagus	3*	—
Hypertensive lower oesophageal sphincter	2	Both had repetitive contractions
Positive edrophonium challenge	6	3* had no other abnormality, 1 had prolonged duration of contractions, 1 had simultaneous contractions, 1 had nutcracker oesophagus

*Total of 31 patients with an oesophageal motility disorder.

had two, three had three, five had four, and one patient had five. Of the 50 hypokinetic segments, 24 were on the anterolateral wall (H_{1-4}) and 26 on the inferior wall (H_{5-7}). The mean (SD) left ventricular ejection fraction of patients with normal regional wall motion (55·4 (4·9)%) was significantly higher than that of patients with hypokinetic segments (43·8 (5·7)%) ($p < 0·001$).

In 28 (44%) patients the results of oesophageal manometry were abnormal (table 1). The most common abnormality was repetitive oesophageal contractions which were usually associated with a prolonged mean duration of contractions. Figure 1 shows an example of a normal manometric study and fig. 2 is a trace from a patient with repetitive oesophageal contractions. In six (10%) patients the usual chest pain developed when abnormal motility developed after intravenous edrophonium; however, three of them had an abnormal basal investigation. Therefore, a total of 31 (49%) patients had abnormal oesophageal motility.

Eleven (21%) patients had an abnormally high 24 hour oesophageal pH score.[18] Ten of these patients had gastro-oesophageal reflux during treadmill exercise testing. In nine of them reflux was associated with their usual chest pain. A further 13 (25%) patients had a normal 24 hour pH score but experienced chest pain coincident with gastro-oesophageal reflux during exercise testing. In each case, the onset of chest pain occurred between one and four minutes after the development of gastro-oesophageal reflux and resolved completely within five minutes of the oesophageal pH returning to >4. These 24 (46%) patients were considered to have gastro-oesophageal reflux disease.[17] Nineteen of these 24 patients also had abnormal oesophageal motility (table 2). Eleven

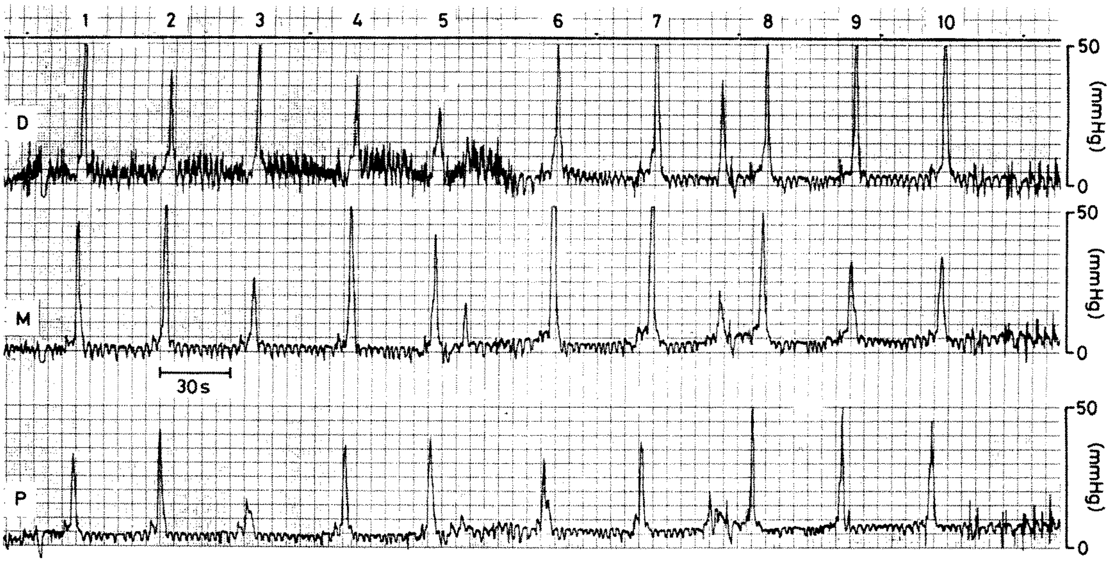

Fig 1 *Normal oesophageal motility with peristaltic contractions of normal amplitude and duration in response to 10 wet swallows. D, distal oesophageal manometer; M, middle oesophageal manometer; P, proximal oesophageal manometer.*

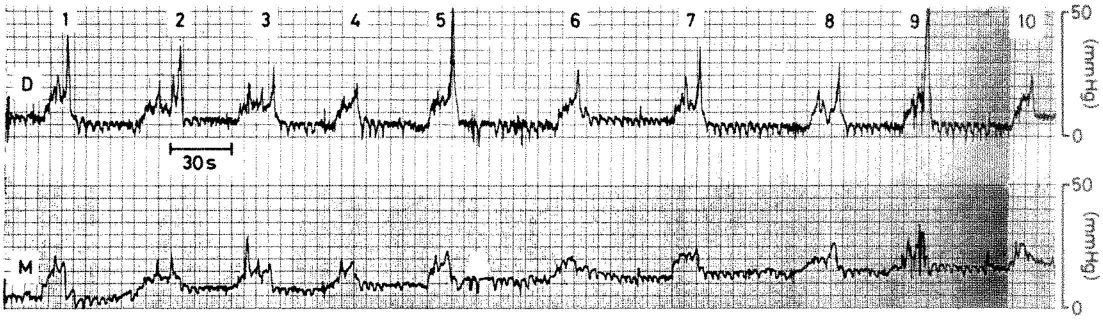

Fig 2 *Abnormal oesophageal motility with repetitive contractions of abnormally long duration (> 6 s) in response to 10 wet swallows. D, distal oesophageal manometer; M, middle oesophageal manometer.*

(46%) patients with gastro-oesophageal reflux disease had both macroscopical and microscopical evidence of oesophagitis and one patient had microscopical evidence of oesophagitis. One patient with a normal oesophageal pH investigation was found to have macroscopical and microscopical oesophagitis and a further two patients had microscopical oesophagitis; all three patients had abnormal oesophageal manometry.

An oesophageal abnormality was therefore demonstrated by manometry or pH monitoring in 36 (57%) (group B) of the 63 patients studied. In 19 patients both investigations were abnormal, in five patients only the pH monitoring was abnormal, and in 12 patients only the manometry was abnormal (including five of the 11 patients who did not undergo oesophageal pH monitoring). Four patients with an oesophageal abnormality also had abnormal regional motion of the left ventricular wall. Only nine (14%) patients (group C) had normal left ventricular function and normal oesophageal pH and manometry.

Table 3 shows the results of the psychiatric assessment. Twenty seven (43%) of the 63 patients in the study were assessed as having a psychiatric disorder. Psychiatric morbidity was significantly less common in patients with left ventricular regional wall motion abnormalities than in patients with an oesophageal abnormality ($p < 0.01$) and patients with normal left ventricular and oesophageal function ($p < 0.05$). There was no difference, however, in psychiatric morbidity between patients with oesophageal abnormalities and those with normal left ventricular and oesophageal function.

Discussion

Previous investigators of patients with "non-cardiac" chest pain have suggested that in some cases symptoms are caused by an oesophageal disorder, including abnormal oesophageal motility[20-24] and gastro-oesophageal reflux.[25,26] Others have demonstrated a high frequency of psychiatric morbidity[5] and we have recently confirmed that some patients have evidence of left ventricular dysfunction.[7] Oesophageal function, left ventricular function, and psychiatric assessment have not previously been examined in the same group of patients. Unlike the present investigation, many previous studies have included patients with atypical chest pain and patients who had not been demonstrated to have *completely* normal coronary angiograms.

We found that 35% of patients had left ventricular regional wall motion abnormalities; this resembles our previous experience.[7] We found that regional abnormalities of wall motion were extremely uncommon in a control group of patients who did not complain of chest pain and had normal coronary angiograms but who did have trivial aortic valve disease.[7] The patients with angina pectoris

Table 2 *Results of oesophageal manometry and endoscopy in 52 patients who underwent oesophageal pH monitoring*

	Oesophageal manometry	*Endoscopy of upper gastrointestinal tract*
Gastro-oesophageal reflux disease (n = 24)	19 abnormal manometry	11 macroscopical and microscopical oesophagitis
	5 normal manometry	1 microscopical oesophagitis
Normal oesophageal pH study (n = 28)	7 abnormal manometry	1 macroscopical and microscopical oesophagitis
	21 normal manometry	2 microscopical oesophagitis

Table 3 *Psychiatric assessment in 63 patients with angina pectoris and normal coronary angiograms*

Description	*Group*	*Psychiatric assessment*
Patients with left ventricular wall motion abnormality (n = 22)	A	4 with psychiatric abnormality, 18 without
Oesophageal abnormality (pH and/or manometry) (n = 36)	B	19 with psychiatric abnormality,* 17 without*
Normal left ventricular and oesophageal function (n = 9)	C	5 with psychiatric abnormality,† 4 without†

*Significantly different from group A, $p < 0{\cdot}01$.
†Significantly different from group A, $p < 0{\cdot}05$.

and normal coronary angiograms who had left ventricular dysfunction, demonstrated features during treadmill exercise testing that were suggestive of myocardial ischaemia[7]; they had a reduced exercise capacity,[27] were more likely to experience chest pain,[28] and had an abnormal ST segment response at an earlier stage of exercise[29] than those with normal left ventricular function. Patients with congestive cardiomyopathy often complain of chest pain, despite the presence of normal or large coronary arteries, and they have been found to have reduced coronary blood flow at rest and during cardiac pacing.[30] No patient in this series had clinical or radiological evidence of cardiac failure. The patients with left ventricular dysfunction were distinct from those with an oesophageal abnormality; only four (6%) patients had both disorders demonstrated.

Although the results of oesophageal manometry were abnormal in many patients with non-cardiac chest pain,[20-24] it has proved difficult to establish a temporal relation between symptoms and the abnormality. This has led to the use of provocation procedures to induce the simultaneous occurrence of chest pain and oesophageal dysmotility; intravenous edrophonium is probably the safest and most effective of these procedures.[13 14] A temporal relation with symptoms was established in 24 (67%) of the 36 patients in this study who had an oesophageal abnormality. In the remaining 12 patients the abnormalities only suggested that the oesophagus was responsible[20] for the chest pain. As well as provocation with intravenous edrophonium during oesophageal manometry we found that treadmill exercise testing during oesophageal pH monitoring helped to confirm the association between symptoms and gastro-oesophageal reflux.[17] The mere presence of an oesophageal abnormality does not indicate a definite causal relation with the patient's chest pain.[31] Although some studies indicate that disordered oesophageal motility is common in patients with coronary artery disease,[32 33] these were studies of small numbers of patients who had oesophageal symptoms[33] and had chest pain other than angina pectoris.[32] We investigated patients with angina pectoris and coronary artery disease and found a low prevalence of oesophageal motility disorder (< 10%, unpublished results). This result increases the likelihood that there is a causal relation in those patients in whom the oesophagus is suspected as a cause of chest pain.

There was no evidence of coronary artery spasm in patients in the present study; however, this is rare in patients with normal coronary arteries[34] and usually produces rest pain rather than exertional chest pain.[35] Rasmussen *et al* have recently demonstrated oesophageal spasm in a small number of patients with coronary artery spasm; some of their patients had important coronary artery disease.[36]

In the present study endoscopy of the upper gastrointestinal tract with oesophageal biopsy found evidence of oesophagitis in 50% of patients who had an abnormality of gastro-oesophageal reflux demonstrated by intra-oesophageal pH monitoring. This is similar to the experience of DeMeester *et al*[25] (39%) and de Caestecker *et al*[26] (38%) and indicates that endoscopy is of limited sensitivity in detecting gastro-oesophageal reflux disease.

Only nine (14%) patients in this series had normal left ventricular function and normal oesophageal pH and manometry. Twenty seven (43%) of the 63 patients had psychiatric morbidity. Bass *et al* assessed psychiatric morbidity in patients with and without coronary artery disease.[37 38] Twenty eight (61%) of 46 patients with normal or near normal coronary arteries had psychiatric morbidity compared with 12 (23%) of 53 patients with important coronary artery disease (> 50% obstruction in one or more vessels). They suggested that psychiatric morbidity in patients with normal or slightly diseased coronary arteries was more likely to be a cause rather than a consequence of chest pain. In this study, psychiatric morbidity was significantly less common in patients with left ventricular dysfunction than in patients with an oesophageal abnormality or patients with normal oesophageal function and normal left ventricular function. The presence of psychiatric morbidity does not, however, exclude the possibility of a left ventricular, an oesophageal, or both abnormalities as the cause of chest pain.

Our findings indicate that patients with typical angina pectoris and completely normal coronary angiograms are heterogeneous in terms of the cause of their symptoms, and that a definite abnormality can be detected in a high proportion. If quantitative assessment of left ventricular function is normal oesophageal disease should be sought. We recommend endoscopy of the upper gastrointestinal tract, and that if no abnormality is detected oesophageal manometry and ambulatory oesophageal pH monitoring (including during treadmill exercise testing) should be performed. A similar policy was advised by de Caestecker *et al*,[26] whereas others have suggested that a psychiatric cause should be considered before oesophageal investigations are undertaken.[31] We hope that accurate diagnosis will lead to effective treatment.

The work described is part of a study that will be submitted by PMS to the University of Manchester for the degree of Doctor of Medicine.

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References

1 Kemp HG, Vokonas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary arteriograms: report of a six year experience. *Am J Med* 1973;54:735–42.

2 Marchandise B, Bourassa MG, Chaitman BR, Lesperance J. Angiographic evaluation of the natural history of normal coronary arteries and mild coronary atherosclerosis. *Am J Cardiol* 1978;41:216–20.

3 Benjamin SB, Castell DO. Chest pain of oesophageal origin. *Arch Intern Med* 1983;143:772–6.

4 Davies HA, Jones DB, Rhodes J. "Oesophageal angina" as the cause of chest pain. *JAMA* 1982;248:2274–8.

5 Bass C, Wade C, Hand D, Jackson G. Patients with angina with normal and near normal coronary arteries: clinical and psychological state 12 months after angiography. *Br Med J* 1983;287:1505–8.

6 Richardson PJ, Livesley B. Oram S. Angina pectoris with normal coronary arteries. Transvenous myocardial biopsy in diagnosis. *Lancet* 1974;ii:677–80.

7 Schofield PM, Brooks NH, Bennett DH. Left ventricular dysfunction in patients with angina pectoris and normal coronary angiograms. *Br Heart J* 1986;56: 327–33.

8 Master AM. The spectrum of anginal and non-cardiac chest pain. *JAMA* 1964;187:894–9.

9 Rackley CE. Quantitative evaluation of left ventricular function by radiographic techniques. *Circulation* 1976;54:862–79.

10 Leighton RF, Wilt SM, Lewis RP. Detection of hypokinesis by a quantitative analysis of left ventricular cineangiograms. *Circulation* 1974;50:121–7.

11 Benjamin SB, Gerhardt DC, Castell DO. High amplitude, peristaltic esophageal contractions associated with chest pain and/or dysphagia. *Gastroenterology* 1979;77:478–83.

12 Benjamin SB, Castell DO. Chest pain of esophageal origin. Where are we, and where should we go? *Arch Intern Med* 1983;143:772–6.

13 Benjamin SB, Richter JE, Cordova CM, Knuff TE, Castell DO. Prospective manometric evaluation with pharmacologic provocation of patients with suspected oesophageal motility dysfunction. *Gastroenterology* 1983;84:893–901.

14 London RL, Ouyang A, Snape WJ, Goldberg S, Hirschfield JW, Cohen S. Provocation of oesophageal pain by ergonovine or edrophonium. *Gastroenterology* 1981;81:10–4.

15 Nelson JL, Wu WC, Richter JE, Blackwell JN, Johns DN, Castell DO. What is normal oesophageal motility? [Abstract]. *Gastroenterology* 1983;84:1258.

16 Berger K, McCallum RW. The hypertensive lower oesophageal sphincter: a clinical and manometric entity [Abstract]. *Gastroenterology* 1981;80:1109.

17 Schofield PM, Bennett DH, Jones PE, *et al*. Exertional gastro-oesophageal reflux. A mechanism for symptoms in patients with angina pectoris and normal coronary angiograms. *Br Med J* 1987;294:1459–61.

18 Johnson LF, DeMeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastro-oesophageal reflux. *Am J Gastroenterol* 1974;62:325–32.

19 Goldberg DP, Cooper B, Eastwood MR, Kedward HB, Shepherd M. A standardized psychiatric interview for use in community surveys. *Br J Prev Soc Med* 1970;24:18–23.

20 Brand DC, Martin D, Pope CE. Esophageal manometrics in patients with angina-like chest pain. *Dig Dis Sci* 1977;22:300–4.

21 Svensson O, Stenport G, Tibbling L, Wranne B. Oesophageal function and coronary angiogram in patients with disabling chest pain. *Acta Med Scand* 1978;204:173–8.

22 Ferguson SC, Hodges K, Hersh T, Jinich H. Esophageal manometry in patients with chest pain and normal coronary arteriogram. *Am J Gastroenterol* 1981;75:124–7.

23 Kline M, Chesne R, Sturdevant RA, McCallum RW. Esophageal disease in patients with angina-like chest pain. *Am J Gastroenterol* 1981;75:116–23.

24 Patterson DR. Diffuse oesophageal spasm in patients with undiagnosed chest pain. *J Clin Gastroenterol* 1982;4:415–7.

25 DeMeester TR, O'Sullivan GC, Bermudez G, Midel AI, Cimochowski GE, O'Drobinak J. Esophageal function in patients with angina-type chest pain and normal coronary angiograms. *Ann Surg* 1982;196:488–98.

26 de Caestecker JS, Blackwell JN, Brown J, Heading RC. The oesophagus as a cause of recurrent chest pain: which patients should be investigated and which tests should be used? *Lancet* 1985;ii:1143–6.

27 Calvert AF, Bernstein L, Bailey IK. Physiological responses to maximal exercise in a normal Australian population: comparative values in patients with anatomically defined coronary artery disease. *Aust NZ J Med* 1977;7:497–506.

28 Cole JP, Ellestad MH. Significance of chest pain during treadmill exercise: correlation with coronary events. *Am J Cardiol* 1978;41:227–32.

29 Kansal S, Roitman D, Bradley EL, Sheffield LT. Enhanced evaluation of treadmill tests by means of scoring based on multivariate analysis and its clinical application: a study of 608 patients. *Am J Cardiol* 1983;52:1155–60.

30 Pasternac A, Noble J, Streulens Y, Elie R, Henschke C, Bourassa MG. Pathophysiology of chest pain in patients with cardiomyopathies and normal coronary arteries. *Circulation* 1982;65:778–89.

31 Channer KS. Oesophageal abnormalities in patients with chest pain. *Lancet* 1986;i:42–3.

32 Brand DL, Martin D, Pope CE. Esophageal manometrics in patients with angina-like chest pain. *Dig Dis Sci* 1977;22:300–4.

33 Tibbling L, Wranne B. Oesophageal dysfunction in male patients with angina-like pain. *Acta Med Scand* 1976;200:391–5.

34 Ginsburg R. Coronary artery spasm: clinical experience and implications. *Hosp Pract* 1983;18:165–76.

35 Mark DB, Califf RM, Morris KG, *et al.* Clinical characteristics and long-term survival of patients with variant angina. *Circulation* 1984;69:880–8.

36 Rasmussen K, Ravnsbaek J, Funch-Jensen P, Bagger JP. Oesophageal spasm in patients with coronary artery spasm. *Lancet* 1986;i:174–6.

37 Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of pyschiatric and social morbidity. *Psychol Med* 1984;14:51–61.

38 Bass C, Wade C, Gardner TN, *et al.* Unexplained breathlessness and psychiatric morbidity in patients with normal and abnormal coronary arteries. *Lancet* 1983;i:605–9.

Br Heart J 1987;58:225–9

Intravenous streptokinase treatment and serum C-reactive protein in patients with acute myocardial infarction

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SUMMARY Serum concentrations of C-reactive protein were studied in 23 patients with acute myocardial infarction. In 14 patients who did not receive thrombolytic treatment there was a linear relation between infarct size (determined by serial creatine kinase-MB determinations and thallium-201 isotope emission tomography) and the C-reactive protein response. The correlation coefficient between the concentration-time integrals of creatine kinase-MB and C-reactive protein was 0·96. The correlation coefficient between the creatine kinase-MB concentration-time integral and the peak serum value of C-reactive protein was 0·93. In the nine patients who received intravenous streptokinase treatment there was also a positive correlation between the concentration-time integrals of creatine kinase-MB and C-reactive protein. The relation, however, depended on the success of the treatment. In patients with successful reperfusion the C-reactive protein response was only approximately 20% of that in patients in whom reperfusion failed or who received no thrombolytic treatment and who were matched by infarct size. When thrombolysis was successful the correlation coefficient between the concentration-time integrals of creatine kinase-MB and C-reactive protein was 0·86.

Daily measurement of serum C-reactive protein is useful in evaluating infarct size in patients with acute myocardial infarction who do not receive thrombolytic treatment. In patients treated with streptokinase C-reactive protein concentrations may be used to assess the success of thrombolysis.

Infarct size is the most important single factor influencing prognosis after acute myocardial infarction,[1 2] but its determination by clinical chemical means is difficult. Total releases of creatine kinase or its MB isoenzyme correlate well with the size of myocardial infarction[3–5] but are difficult to measure in routine clinical work. C-reactive protein is synthesised in the liver and its synthesis is stimulated by a number of diseases, including acute myocardial infarction.[6] It has been shown that the rise in C-reactive protein during infarction correlates with the activity of serum creatine kinase-MB,[7] but the correlation of C-reactive protein with infarct size has as yet been little studied. We found that serum C-reactive protein may not rise in certain non-Q wave infarcts.[8] Most non-Q wave infarcts result from an acute temporary imbalance between myocardial oxygen supply and demand with rapid restoration of adequate perfusion.[9] Rapid perfusion of an infarcted myocardium could diminish the stimulus for C-reactive protein synthesis in the liver by altering the development of the infarction. If this is the case, successful thrombolytic treatment of an acute myocardial infarct should have a similar effect.

We studied serum concentrations of C-reactive protein in both streptokinase and non-streptokinase treated patients with acute myocardial infarction.

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Patients and methods

We studied 23 patients (mean (SD) age 56 (10) years) with a first acute myocardial infarction. The patients were selected for the study according to the following criteria: acute chest pain and arrival at the hospital within four hours of onset of pain, diagnostic ST segment elevations in the first electrocardiogram that did not disappear after treatment with glyceryl trinitrate, and subsequent development into diagnostic Q waves.

Nine patients (mean (SD) age 53 (7)) received high dose (1·8 million units) intravenous streptokinase given over an hour. In seven of the nine streptokinase treated patients reperfusion was considered successful as judged by indirect criteria of reperfusion: early peaking of total serum creatine kinase and creatine kinase-MB values (13 (2) h and 11 (2) h respectively), relief of chest pain, and improvement in electrocardiographic ST shifts. Six patients had arrhythmias typical of reperfusion. In two patients reperfusion was considered to have failed because of late peak values of creatine kinase (24 and 28 h) and creatine kinase-MB (20 and 24 h) and continuing chest pain after streptokinase infusion. Although indirect means were used to evaluate the success of reperfusion, coronary angiography was undertaken in all patients two to four weeks later. In the two patients in whom reperfusion was not considered to have taken place there was occlusion of the infarct related coronary artery, whereas in the others a variable degree of coronary atherosclerosis was noted but without occlusion of any of the coronary arteries. Because streptokinase treatment was not started in our hospital until after the start of the present study only nine patients were given streptokinase.

Blood samples were taken immediately on arrival and 2 (when feasible), 4, 6, 8, 12, 24, 32, and 48 hours after the onset of chest pain and then daily until discharge or for two weeks. The samples were analysed for total creatine kinase and creatine kinase-MB activities (reference values 0–250 U/l and 0–25 U/l, respectively) as well as C-reactive protein concentrations (0–10 mg/l). The activity of creatine kinase was determined at 37°C according to the recommendations of the Scandinavian Committee on Enzymes.[10,11] The creatine kinase-M moiety was inhibited with M-specific antibodies[12] and the remaining creatine kinase activity (creatine kinase-MB moiety) was determined at 37°C with the same reagents (from Boehringer Mannheim, Federal Republic of Germany) as in the assay of total creatine kinase. Total creatine kinase, creatine kinase-B, and C-reactive protein[13] were measured with a Hitachi 705 analyser (Oriola Oy, Espoo, Finland).

Thallium-201 isotope emission tomography with a rotating gamma camera (GE 400T Maxicamera, tomography software from Nuclear Diagnostics, Sweden) was carried out at rest during the second week after the onset of pain. The volume of infarction was calculated by a semiautomatic computer program from a set of short axis pictures. In this method an absolute scaling from a slice (with a thickness of 13 mm) was first carried out. Then the estimated inner and outer contours of the left ventricle and the contour of the intact myocardium were delineated. The difference between these areas was taken to represent the scar tissue in this particular slice of heart. The total volume of the infarct in millilitres was then estimated by summing the results from all slices.

We used regression analysis and calculation of the correlation coefficient for statistical analysis.

Results

In all patients (both those treated conventionally and those treated with streptokinase) there was a good correlation between the areas under the creatine kinase-MB curves (concentration-time integral) and the results of thallium-201 isotope emission tomography (r = 0·72; p < 0·001; fig 1) and the relation

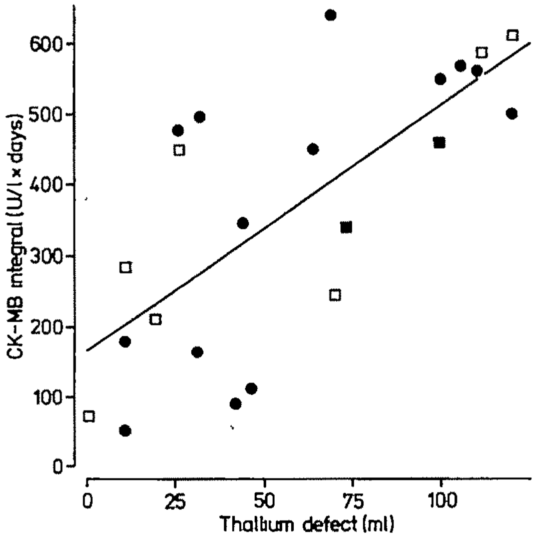

Fig 1 *Relation between creatine kinase-MB (CK-MB) concentration-time integral (U/l × days) and defect (ml) estimated by thallium-201 isotope emission tomography.* ●, *conventionally treated patients;* □, *streptokinase treated patients with reperfusion;* ■, *streptokinase treated patients without reperfusion. The correlation coefficient of the data from all patients is 0·72 (p < 0·001) and the equation of the regression line is* $y = 3{\cdot}6x + 160$ *(p < 0·001).*

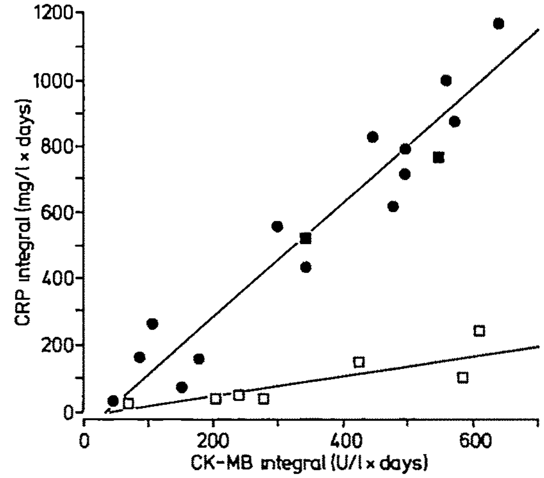

Fig 2 *Relation between C-reactive protein (CRP) concentration-time integral (mg/l × days) and creatine kinase-MB (CK–MB) concentration time integral (U/l × days).* ●, *conventionally treated patients;* □, *streptokinase treated patients with reperfusion;* ■, *streptokinase treated patients without reperfusion. The correlation coefficient for the data from the conventionally treated patients was 0·96 (p < 0·001) and the equation of the regression line (the upper line in the figure) is y = 1·8x − 72 (p < 0·001). The correlation coefficient for the data from the patients with a successful streptokinase treatment is 0·86 (p < 0·05) and the equation of the regression line (the lower line in the figure) is y = 0·4x − 40 (p < 0·05).*

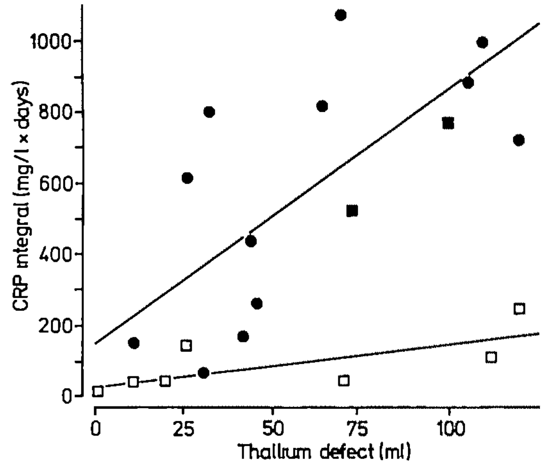

Fig 3 *Relation between C-reactive protein (CRP) concentration-time integral (mg/l × days) and defect (ml) estimated by thallium-201 isotope emission tomography.* ●, *conventionally treated patients;* □, *streptokinase treated patients with reperfusion;* ■, *streptokinase treated patients without reperfusion. The correlation coefficient for the data from conventionally treated patients is 0·69 (p < 0·01) and the equation of the regression line (the upper line in the figure) is y = 7·2 × 156 (p < 0·01). The correlation coefficient for the data from the patients with a successful streptokinase treatment is 0 67 (NS) and the equation of the regression line is y = 1.2x + 32 (NS).*

did not depend on the success of streptokinase treatment.

In those patients who were not given streptokinase treatment the peak serum values of creatine kinase-MB and C-reactive protein correlated positively with each other (r = 0·89; p < 0·001). The correlation was improved if concentration-time integrals were used instead of peak serum concentrations (r = 0·96; p < 0·001, fig 2). The peak value of serum C-reactive protein correlated with the concentration-time integral of creatine kinase-MB at least as

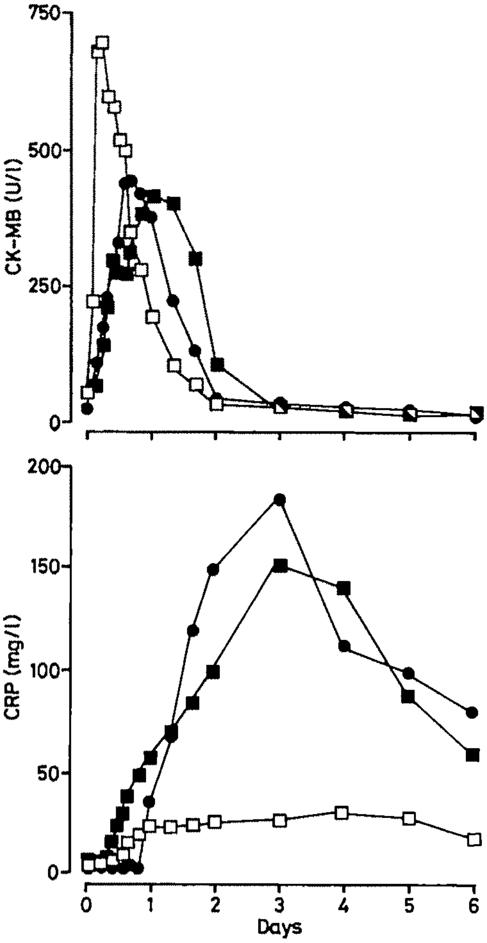

Fig 4 *Change in concentrations of serum C-reactive protein (CRP) and creatine kinase-MB (CK–MB) with time after the onset of chest pain in three patients with an anterior wall myocardial infarction.* ●, *a conventionally treated patient;* □, *a streptokinase treated patient with reperfusion;* ■, *a streptokinase treated patient without reperfusion. The volumes (ml) of defects estimated by thallium-201 isotope emission tomography were 106, 112, and 119 and the concentration-time integrals of creatine kinase-MB (U/l × days) were 571, 585, and 549 respectively.*

well as the peak value of serum creatine kinase-MB itself did (r = 0·93 and 0·91, respectively). The correlation between the peak C-reactive protein value and C-reactive protein concentration-time integral was 0·96. There was also a positive correlation between the thallium-201 isotope emission tomography results and the C-reactive protein response ($r = 0{\cdot}69$; $p < 0{\cdot}01$; fig 3).

If the patients were treated with intravenous streptokinase and reperfusion was achieved the C-reactive protein response was less than 20% of that in patients who did not receive thrombolytic treatment and were matched by infarct size according to creatine kinase-MB concentration-time integral and thallium-201 isotope emission tomography defect (figs 2 and 3). There was still a positive correlation between infarct size and the C-reactive protein response. If reperfusion was not achieved the response of C-reactive protein was similar to that in patients not treated with streptokinase (figs 2 and 3).

Figure 4 shows the C-reactive protein and creatine kinase-MB curves of three patients with an anterior wall myocardial infarction matched by infarct size according to thallium-201 emission tomography defect and creatine kinase-MB concentration-time integral. This shows that the C-reactive protein responses of the patients in whom there was no reperfusion were similar, whereas the patient with successful reperfusion showed hardly any C-reactive protein response despite his large infarct. The patient with successful reperfusion felt considerably better than the other two in the first three days after infarction. Indeed, successful thrombolytic treatment tended to be associated with clinical wellbeing even if infarct size was not reduced. This sense of wellbeing seemed to correlate with the reduction in the rise in serum C-reactive protein concentration that was associated with the acute phase of infarction.

Discussion

The present study assessed the value of serum C-reactive protein as an estimate of infarct size. Like De Beer *et al*[7] we found a good correlation between the peak serum concentrations of creatine kinase-MB and C-reactive protein in patients not receiving thrombolytic treatment. The correlation was improved and the scatter was reduced if concentration-time integrals were used instead of peak values. Previous studies have shown that the concentration-time integral of creatine kinase-MB is a reliable estimate of infarct size.[3–5] We too found that the concentration-time integral of C-reactive protein correlated well with the results of thallium-201 isotope emission tomography.

It is not convenient to calculate concentration-time integrals in routine clinical work or to sample blood often enough to determine reliably the peak serum concentration of creatine kinase-MB, which is usually reached 8–30 h after the onset of an acute myocardial infarct.[14] Serum C-reactive protein rises more slowly in the course of acute myocardial infarction[8] and according to our present and previous results[8] routine daily blood sampling seems to permit reliable detection of its peak serum concentrations. The good correlation between the peak serum value of C-reactive protein and its concentration-time integral means that peak values are a useful way of estimating infarct size by laboratory means. Conditions other than myocardial infarction raise the concentration of serum C-reactive protein[6] and these may occasionally interfere with the determination of infarct size. This was not a problem in our patients. Although some non-Q wave infarcts are not associated with a rise in C-reactive protein, we do not think that this will lessen the value of the determination of C-reactive protein in acute myocardial infarction.

In patients treated with intravenous streptokinase the rise in serum C-reactive protein depended on the success of thrombolysis as well as the infarct size. When reperfusion was successful there was only a modest rise in serum C-reactive protein even if the resultant myocardial infarction was large as judged by creatine kinase-MB concentration-time integral and the defect displayed by thallium-201 isotope emission tomography. With the possible exception of the smallest myocardial infarcts the measurement of serum C-reactive protein seems to permit the success of reperfusion after intravenous streptokinase treatment to be evaluated.

The reason for the modest response of C-reactive protein after successful thrombolytic treatment is not at present clear. When thrombolysis was not successful, the behaviour of serum C-reactive protein was similar to that in patients who had not received streptokinase treatment. This makes it unlikely that streptokinase itself or fibrinogen degradation products influenced the synthesis of C-reactive protein in the liver. Serum C-reactive protein does not rise in certain non-Q wave infarcts with features of subendocardial infarcts.[8] It has been postulated that an adequate coronary blood flow is often rapidly restored in subendocardial infarcts[9]: a situation resembling a successful reperfusion with streptokinase. It may be that a rapid reperfusion of the infarcted myocardium changes the evolution of infarction in such a way that the usual acute phase reaction does not take place. This may have clinical implications, and, indeed, the patients with reperfusion by intravenous streptokinase fared much better clinically than those with no reperfusion or thrombolytic treatment. This was true even if the patients were matched by infarct size as determined by the creatine kinase-MB concentration-time integral and the defect measured by thallium-201 isotope emission tomography. A more detailed study of the effect on the acute phase reaction on the clinical outcome seems warranted.

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References

1 Mock MB, Ringqvist I, Fiscger LD *et al.* Survival of medically treated patients in the coronary artery surgery study (CASS) registry. *Circulation* 1982;**66**:562–8.

2 Kelly MJ, Thompson PL, Quinlan MF. Prognostic significance of the left ventricular ejection fraction after acute myocardial infarction. A bedside radionuclide study. *Br Heart J* 1985;**53**:16–24.

3 Rogers WJ, McDaniel HG, Smith LR, *et al.* Correlation of angiographic estimates of myocardial infarct size and accumulated release creatinine kinase isoenzyme in man. *Circulation* 1977;**56**:199–205.

4 Henning H, Schelberg HR, Righetti A, *et al.* Dual myocardial imaging with technetium-99m pyrophosphate and thallium-201 for detecting, localising and sizing acute myocardial infarction. *Am J Cardiol* 1977;**147**:147–55.

5 Grande P, Hansen BF, Christiansen C, Waestoff J. Estimation of acute myocardial infarct size by serum CK-MB measurements. *Circulation* 1982;**65**:756–64.

6 Pepys MB. C-reactive protein fifty years on. *Lancet* 1981;**i**:653–7.

7 de Beer FC, Hind CRK, Fox KM, Allan RM, Maseri A, Pepys MB. Measurement of serum C-reactive protein in myocardial ischaemia and infarction. *Br Heart J* 1982;**47**:239–43.

8 Pietilä K, Harmoinen A, Pöyhönen L, Ruosteenoja R. C-reactive protein in subendocardial and transmural myocardial infarcts. *Clin Chem* 1986;**8**:1596–7.

9 Laeffel GL, Braunwald E. Thrombolytic therapy. A new strategy for the treatment of acute myocardial infarction (first of the two parts). *N Engl J Med* 1984; **311**:710–7.

10 The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of creatinine kinase in blood. *Scand J Clin Lab Invest* 1976;**36**:711–23.

11 The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Experiences with the Scandinavian recommended methods for the determination of enzymes in blood. *Scand J Clin Lab Invest* 1981;**41**:107–16.

12 Würzburg U, Hennrich N, Lang H, *et al.* Bestimmung der Aktivität von Creatinkinase MB in Serum unter Verwendung inhibierender Antikröper. *Klin Wochenschr* 1976;**54**:357–60.

13 Harmoinen A. Immunoassay of C-reactive protein using the Hitachi 705E analyzer. *J Clin Chem Clin Biochem* 1985;**23**:45–6.

14 Ong L, Reiser P, Coromilas J, *et al.* Left ventricular function and rapid release of creatine kinase MB in acute myocardial infarction: evidence for spontaneous reperfusion. *N Engl J Med* 1983;**309**:1–6.

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Total body electrolyte composition in patients with heart failure: a comparison with normal subjects and patients with untreated hypertension

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SUMMARY Total body elemental composition was measured in 40 patients with well documented heart failure who were oedema-free on digoxin and diuretics. The results were compared with values for 20 patients with untreated essential hypertension matched for height, weight, age, and sex. Total body potassium alone was also measured in 20 normal subjects also matched for anthropomorphic measurements. Patients with hypertension had a very similar total body potassium content to that of normal subjects, but patients with heart failure had significantly reduced total body potassium. This could not be explained by muscle wasting because total body nitrogen, largely present in muscle tissue, was well maintained. When total body potassium was expressed as a ratio of potassium to nitrogen mass a consistent depletion of potassium was revealed in the group with heart failure. Potassium depletion was poorly related to diuretic dose, severity of heart failure, age, or renal function. Activation of the renin-angiotensin-aldosterone system was, however, related to hypokalaemia and potassium depletion. Such patients also had significantly lower concentrations of serum sodium and blood pressure. Serum potassium was related directly to total body potassium. Despite the absence of clinically apparent oedema total body chlorine was not consistently increased in heart failure, but the calculated extracellular fluid volume remained expanded in the heart failure group. Total body sodium was significantly increased in patients with heart failure, but less than half of this increase could be accounted for by extracellular fluid volume expansion.

Potassium depletion in heart failure may account in part for the high frequency of arrhythmias and sudden death in this condition.

After many years of debate there is still controversy about the prevalence, extent, and relevance of potassium depletion in patients treated with diuretics for heart failure.[1–6] Reports of reduced body potassium in such patients have been attributed to lack of good control data or to muscle wasting in "cardiac cachexia."[1] Some of the difficulty may have arisen because of the absence of a definitive diagnosis of heart failure, which has largely been resolved by new diagnostic techniques, in particular echocardiography. Also, the measurement of total exchangeable potassium requires a prolonged equilibration time after the administration of radioactive tracers and this can introduce inaccuracies.[5,7] Measurement of total body potassium by the endogenous ^{40}K isotope avoids this difficulty. It is also difficult to define adequate control groups for comparison. Body elemental composition is highly dependent on body mass, adiposity, age, and sex.[8] Control groups have rarely been adequately matched with patients in heart failure, nor have appropriate corrections usually been made.

Patients with severe heart failure have a poor prognosis, the one year survival for a patient with

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New York Heart Association grade III heart failure being approximately 60%.[9,10] Interest in potassium depletion in heart failure was renewed by the observation that potassium depletion can be corrected, arrhythmias reduced, and possibly prognosis improved by angiotensin converting enzyme inhibitors.[11,12]

The technique of in vivo total body neutron activation analysis performed on the same day for all elements also has allowed us to measure total body sodium, chlorine, phosphorus, calcium, and nitrogen. Nitrogen is an index of protein mass[13]—muscle, collagen, and the viscera being the major sites of this element.[14] Measurement of body nitrogen allows us to correct for leanness. In vivo neutron activation analysis requires a dose of radiation that cannot be justified in normal subjects. We used endogenous ^{40}K measurements followed by activation analysis to assess body composition in untreated patients with essential hypertension,[15] which does not differ from normal values. We have also measured total body potassium in a large series of normal subjects and found no difference from the mean value in patients with untreated essential hypertension who were matched for age and sex.[16,17] We have therefore compared patients treated for heart failure with diuretics and digoxin with patients with untreated essential hypertension and with normal subjects matched for height, weight, age, and sex.

Patients and methods

PATIENTS

Forty patients referred to the cardiac department for further investigation and treatment of heart failure were compared with 20 subjects without evidence of cardiac or other disease and 20 patients with untreated essential hypertension. Heart failure was confirmed by the measurement of a raised left ventricular end diastolic pressure (> 16 mm Hg) and poor stroke volume on left ventricular cineangiography, with a fractional shortening on M mode echocardiography of less than 20% (14 (3)%, mean (SEM)) and end diastolic dimension greater than 6 cm (6·4 (0·2) cm). The aetiology of cardiac failure was ischaemic heart disease in 20, idiopathic (dilated cardiomyopathy in 17, and severe residual left ventricular dysfunction after successful valve replacement in three (two aortic, one mitral and aortic). Nine were in early heart failure (New York Heart Association class IV) but did not suffer undue orthopnoea, 18 in class III, and 13 in class II. All patients had received at least 80 mg/day of frusemide (mean 147 (13) mg/day) for more than three months (mean (SEM) duration 11 (5) months). In addition to frusemide, five were taking bendrofluazide 5–10 mg/day. Twelve were taking potassium chloride in a mean daily dose of 2·1 (0·1) g, but none was taking potassium-sparing diuretics.

Table 1 shows the mean blood pressure in the groups with hypertension and heart failure. All those with hypertension were symptom free without clinical, biochemical, or radiological features of heart failure, aortic coarctation, Cushing's syndrome, primary hyperaldosteronism, renal disease, or phaeochromocytoma. Any previous treatment had been withdrawn at least four weeks before the measurements were made.

METHODS

We measured nude weight and height in each subject. Blood pressure was recorded in supine patients by a standard sphygomomanometer with phase V as the diastolic pressure. Total body potassium was measured by whole body counting of endogenous ^{40}K before irradiation.[18]

Total body sodium, chlorine, calcium, phos-

Table 1 *Comparison of total body potassium in normal subjects and in patients with hypertension and heart failure*

	Normal (16M/20F) *Mean*			*Hypertension (15M/20F)* *SEM*			*Heart failure (32M/40F)* *Range*		
	Normal	*Hypertension*	*Heart failure*	*Normal*	*Hypertension*	*Heart failure*	*Normal*	*Hypertension*	*Heart failure*
Age (years)	52	53	56	3	3	1	31–72	30–71	28–64
Height (cm)	170	168	167	2	2	1	154–184	151–186	146–180
Weight (kg)	69	69	68	2	3	2	47–92	44–109	45–88
Total body potassium (mmol)	3208	3250	2831*†	131	171	93	2315–4274	2043–4951	1518–4031
Total body nitrogen (g)	1642	1640	1688	51	59	49	1239–2093	1128–2109	1090–2285
Total body potassium nitrogen ratio (mmol:g)	1·95	1·97	1·68‡§	0·04	0·05	0·03	1·67–2·35	1·54–2·35	1·34–2·09

*p 0·02 *vs* normal; †p 0·05 *vs* hypertension; ‡p 0·0001 *vs* normal; §p 0·0001 *vs* hypertension.

phorus, nitrogen, and oxygen were measured simultaneously by activation with 14 MeV neutrons followed by whole body counting[19–25] in the two patient groups only. The radiation dose was not justified in normal subjects. In normal subjects total body nitrogen was predicted from anthropomorphic measurements. During total body in vivo neutron activation analysis (TBIVAA) the patient lay on a bed which was driven between two neutron generators and received a radiation dose equivalent of 1 rem (10 mSv) at the body surface. Induced radioactivity was then measured in a high sensitivity shadow shielded whole body counter by two sodium iodide detectors with repeated counting scans for up to 30 minutes after irradiation. The calibration and reproducibility of these measurements are described elsewhere, but replicate measurements are generally within 3%.[19 21 22] Values are expressed in mmol for sodium, potassium, and chlorine; in grams for calcium, phosphorus, and nitrogen, and in kilograms for oxygen. Values were also expressed as a percentage of the predicted normal. The normal values for total body potassium are predicted from those obtained by Boddy *et al*,[18] in a large series of normal subjects at our own facility, and based on height, weight, age, and sex. To predict total body sodium and calcium we used equations derived from neutron activation analysis measurements in normal subjects made by Ellis *et al*[24 25] that relate total body in vivo neutron activation analysis measurements to height, weight, age, and sex. Equations for the prediction of total body chlorine values were based on measurements of extracellular fluid volume made with radioactive bromine.[26] Extracellular fluid volume was calculated from total body chlorine and serum chloride.[27] "Dry" weight also was estimated for the heart failure group by correcting their weight to the same extracellular fluid volume per kg as the hypertensive group. Predicted values for total body nitrogen were derived from the formula $N\ (g) = 322 \times \text{height}^3 + 81$ in hypertensive subjects; this is regarded as an accurate method of prediction.[15] Potassium was also expressed as mmol/g of nitrogen as suggested by Burkinshaw and Morgan.[28]

Since phosphorus was not measured in normal subjects, and as the amounts of calcium and phosphorus are normally closely related, the ratio (P/Ca) was used.[15] Total body oxygen in normal subjects has not been measured by this technique.

Blood was drawn at 9 am from fasting patients who had been supine overnight and again at 4 pm in patients who had been supine for 30 minutes. Sodium, potassium, chloride, urea, creatinine, and phosphate were measured and the results were

Table 2 *Comparison of measurements in patients with hypertension and heart failure*

	Hypertension	*Heart failure*	*p*
Weight (kg)	69 (3)	68 (2) 67 (3) (corrected for ECF)	NS
Mean blood pressure (mm Hg)	126 (3)	94 (3)	< 0·001
Serum sodium (mmol/l)	141 (1)	138 (1)	< 0·05
Serum potassium (mmol/l)	4·2 (0·1)	3·6 (0·1)	< 0·005
Serum chloride (mmol/l)	102 (1)	98 (1)	< 0·05
Serum bicarbonate (mmol/l)	27·5 (0·5)	29·3 (0·4)	< 0·02
Serum urea (mmol/l)	4·7 (0·3)	6·6 (0·4)	< 0·005
Serum creatinine (µmol/l)	90 (3)	102 (4)	< 0·05
Urea:creatinine ratio	51·7 (0·2)	64·4 (2·7)	< 0·005
PARC (µU/ml)	24 (5)	215 (46)	< 0·005
Plasma angiotensin II (pmol/l)	23 (1)	64 (9)	< 0·005
Plasma aldosterone (pmol/l)	331 (32)	729 (117)	< 0·005
Total body potassium (mmol)	3250 (171)	2831 (93)	< 0·05
Total body potassium (%)	103 (89–110)	95 (67–117)*	< 0·01
Total body nitrogen (g)	1640 (59)	1688 (49)	NS
Total body nitrogen (%)	100 (92–117)	106 (86–133)†	NS
Total body potassium.nitrogen (mmol:g)	1·97 (0·05)	1·68 (0·03)	< 0·0001
Total body potassium.nitrogen (%)	103 (97–108)	91 (74–106)‡	< 0·001
Total body sodium (mmol)	3160 (113)	3473 (88)	< 0·05
Total body sodium (%)	98 (89–104)	108 (92–129)	< 0·001
Total body chlorine (mmol)	1697 (70)	1748 (55)	NS
Total body chlorine (%)	96 (86–110)	104 (87–142)	NS
Extracellular fluid volume (ml)	16·7 (0·6)	17·9 (0·5)	NS
Extracellular fluid volume (ml/kg)	242 (9)	266 (6)	< 0·02
Total body calcium (g)	960 (37)	998 (23)	NS
Total body calcium (%)	98 (89–112)	106 (83–121)†	NS
Total body phosphorus (g)	534 (20)	542 (13)	NS
Total body phosphorus:calcium (g:g)	0·56 (0·01)	0·54 (0·01)	< 0·02

ECF, extracellular fluid volume; %, percentage of normal predicted; PARC, plasma active renin concentration

*p < 0·05, †p < 0·001, ‡p < 0·001 compared with predicted normal (see text)

Values are mean (SEM) for absolute values and mean and range for percentage values.

expressed as the mean of the two values. Plasma concentrations of active renin, angiotensin II, and aldosterone were measured in the 9 am sample.[29-32]

STATISTICAL ANALYSIS

For group analysis we used Student's *t* test or the Wilcoxon rank sum test for non-parametrically distributed variables. Results for patients with heart failure and hypertension were expressed as the ratio of calculated to predicted normal, 100% representing no difference between calculated and predicted values. A single parameter *t* test was used to test for systematic deviation from predicted values. We used a 5% level of significance. Correlations were performed by the method of least squares for variables with bivariate normal distribution and by Spearman's rank correlation for non-parametrically distributed data.

Results

ANTHROPOMORPHIC MEASUREMENTS (TABLE 1)

The normal subjects and patients with hypertension and heart failure were similar with respect to height, weight, age, and sex. Subgroups of heart failure patients with normal and raised renin were similar, and neither group differed from the normal or hypertensive group. The similarity in weight persisted even when the weight of the heart failure groups was corrected for the higher extracellular fluid volume (table 2).

BLOOD PRESSURE (TABLE 2)

Though the blood pressure in the hypertensive group was not greatly raised (170 (3)/105 (3) mm Hg) mean blood pressure was significantly greater than in those with heart failure (132 (2)/78(1)).

SERUM ELECTROLYTES (TABLE 2)

Serum sodium, potassium, and chloride were significantly higher in those patients with hypertension, while serum bicarbonate, urea, and creatinine were higher in those with heart failure.

HORMONES (TABLE 2)

Plasma concentrations of active renin, angiotensin II, and aldosterone were considerably higher in subjects with heart failure. Only two subjects with hypertension had plasma active renin concentration outside the normal range compared with 26 patients with heart failure.

TOTAL BODY COMPOSITION (TABLES 1–3)

Total body potassium was lower in patients with heart failure than in normal controls, the hypertensive group, and the predicted normal values. Total body potassium was normal in the hypertensive group as previously reported. Mean total body sodium was normal in the hypertensive group but raised in the group with heart failure compared with the hypertensive group or with predicted normal values. Total body chlorine was not significantly different in the two groups and did not deviate significantly from the predicted value. Although total extracellular fluid volume was similar in hypertensive patients and patients with heart failure, when results were corrected for body weight, patients with heart failure had a significantly expanded volume despite being free from clinically apparent oedema. Total body calcium was higher in patients with heart failure but the value for phosphorus was similar in both groups of patients. The ratio of phosphorus to calcium was consequently lower in the patients with heart failure.

Absolute values for total body nitrogen were similar in the heart failure group, normal controls, and hypertensive patients. When expressed as a percentage of predicted normal, nitrogen values were increased only in the heart failure group. The difference in potassium expressed in mmol/g of nitrogen was thus highly significant; values were much lower in those with heart failure. After correction for nitrogen values subjects with heart failure were approximately 12% depleted of potassium compared with hypertensive patients.

COMPARISON OF SUBGROUPS OF CARDIAC FAILURE PATIENTS WITH LOW OR NORMAL RENIN CONCENTRATIONS AND THOSE WITH RAISED CONCENTRATIONS (TABLE 4)

We used a cut off point of 50 μU/ml for plasma active renin concentration; this was the upper limit of normal for our laboratory. Subjects in each group were well matched for anthropomorphic measurements, though the high renin group had an excess of men. The patients with high plasma renin (n = 26) had correspondingly high plasma concentrations of angiotensin II and aldosterone. There was no difference in the severity of heart failure or diuretic requirements between the groups. Total body and serum potassium, serum sodium, and mean blood pressure were all inversely related to plasma renin (figs 1–4). Potassium supplements were significantly greater in those subjects with low serum potassium and raised plasma renin. Extracellular fluid volume was not contracted in those with a high plasma renin. Only two hypertensive patients had raised plasma renin.

CORRELATIONS BETWEEN SERUM AND TOTAL BODY ELECTROLYTES

Serum and total body potassium (expressed as a per-

Table 3 *Total body oxygen in patients with hypertension and patients with heart failure*

	Hypertension	*Heart failure*	*p*
No	7	32	
Total body oxygen (kg)	42·9 (3·0)	36·0 (2·3)	< 0·05
Total body oxygen (%)	104 (89–112)	93 (76–109)	< 0·01
Total body oxygen (kg/kg body weight)	0·59 (0·05)	0·54 (0·07)	< 0·01
TBK/TBO (mmol/kg)	80 (5)	79 (9)	NS
TBNa/TBO (mmol/kg)	79 (8)	95 (9)	< 0·001

TBO, total body oxygen; TBK, total body potassium; TBNa, total body sodium; %, percentage of predicted normal.
Values are mean (SEM) for absolute values and mean (range) for percentage values.

Table 4 *Comparison of measurements in patients with heart failure and with normal or high renin concentrations*

	Renin <50 μU/ml	*Renin >50 μU/ml*	*p*
Proportion of men to total	9/14	23/26	NS
Age (years)	58 (1)	55 (2)	NS
Height (cm)	163 (3)	168 (1)	NS
Weight (kg)	67 (3)	68 (2)	NS
NYHA	3 (2–4)	3 (2–4)	NS
Frusemide (mg/day)	124 (16)	158 (18)	NS
Bendrofluazide	2 patients	3 patients	
Potassium chloride (mg/day)	343 (0–1200)	1080 (0–2040)	< 0·05
Mean blood pressure (mm Hg)	109 (4)	87 (2)	< 0·001
Serum sodium (mmol/l)	141 (1)	137 (1)	< 0·01
Serum potassium (mmol/l)	4·0 (0·1)	3·5 (0·1)	< 0·001
Serum chloride (mmol/l)	100 (1)	97 (2)	NS
Serum bicarbonate (mmol/l)	29 (1)	29 (1)	NS
Serum urea (mmol/l)	6·2 (0·4)	6·8 (0·6)	NS
Serum creatinine (μmol/l)	101 (7)	103 (5)	NS
Urea:creatinine ratio	60 (2)	70 (2)	NS
PARC (μU/ml)	33 (4)	313 (62)	
Plasma angiotensin II (pmol/l)	20 (3)	87 (12)	< 0·001
Plasma aldosterone (pmol/l)	272 (31)	975 (160)	< 0·001
Total body potassium (%)	105 (95–117)*	91 (67–104)†	< 0·01
Total body nitrogen (%)	109 (90–133)*	104 (86–116)*	NS
Total body potassium:nitrogen (mmol:g)	1·78 (0·05)	1·63 (0·03)	< 0·01
Total body potassium:nitrogen (%)	97 (94–106)	88 (74–98)†	< 0·01
Total body sodium (%)	110 (96–129)*	105 (92–118)*	NS
Total body chlorine (%)	107 (88–142)	103 (87–120)	NS
Extracellular fluid volume (ml/kg)	260 (9)	270 (9)	NS
Total body calcium (%)	106 (86–118)	104 (83–121)*	NS
Total body phosphorus:calcium	0·54 (0·01)	0·59 (0·04)	NS
Total body oxygen (kg/kg body weight)	0·53 (0·05)	0·54 (0·08)	NS

NYHA, New York Heart Association class; %, percentage of normal predicted; PARC, plasma active renin concentration.
*p <0·01, †p < 0·001 compared with predicted normal (see text).
Values are mean (SEM) for absolute values and mean and range for percentage values.

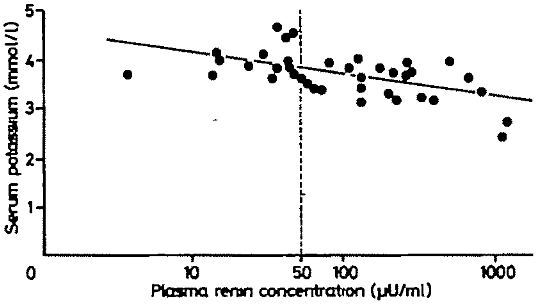

Fig 1 *Relation between plasma active renin concentration (expressed on a log scale) and serum potassium in patients with heart failure. (r = −0·57; p < 0·001; n = 40). Two points in the central cluster of the diagram completely overlap and only 38 points are actually visible.*

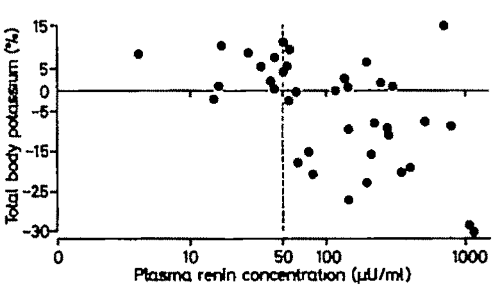

Fig 2 *Relation between plasma active renin concentration (expressed on a log scale) and total body potassium (expressed as a percentage of prediced normal) in patients with heart failure. (Spearman's R = −0·51; p < 0·01; n = 38).*

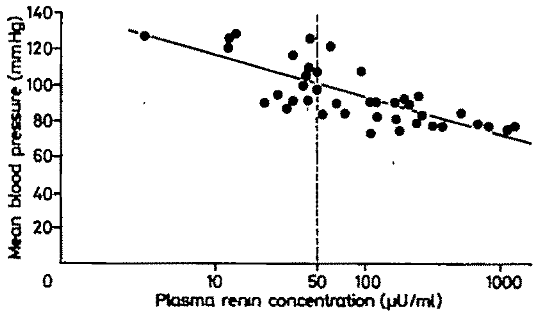

Fig 3 *Relation between plasma active renin concentration (expressed on a log scale) and mean blood pressure in patients with heart failure.* ($r = -0{\cdot}76$; $p < 0{\cdot}001$; $n = 40$).

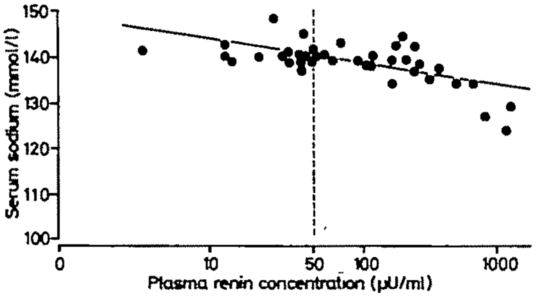

Fig 4 *Relation between plasma active renin concentration (expressed on a log scale) and serum sodium in patients with heart failure.* ($r = -0{\cdot}67$; $p < 0{\cdot}001$; $n = 40$).

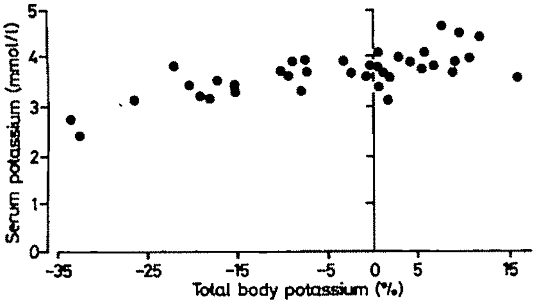

Fig 5 *Relation between total body potassium (expressed as a percentage of predicted normal and serum potassium in patients with heart failure.* (Spearman's $R = -0{\cdot}72$; $p < 0{\cdot}001$; $n = 38$).

centage of predicted normal) were significantly correlated ($r = 0{\cdot}72$; $p < 0{\cdot}001$) (fig 5) and this relation was maintained after correcting total body potassium for total body nitrogen ($r = 0{\cdot}75$; $p < 0{\cdot}001$). The relation appeared linear over the measured range. A similar relation was not observed in the group with hypertension ($r = 0{\cdot}1$; NS and $r = 0{\cdot}3$; NS). Serum sodium ($r = 0{\cdot}1$ heart failure and $r = 0{\cdot}36$ hypertension) was not significantly related to total body sodium (percentage of predicted normal) but serum chloride was related to total body chlorine (percentage of predicted normal ($r = 0{\cdot}34$; $p < 0{\cdot}05$ heart failure and $r = 0{\cdot}59$; $p < 0{\cdot}01$ hypertension).

Discussion

HYPERTENSION

Hypertensive subjects have similar mean values for body element composition as normal subjects.[15, 16] The present study confirmed that total body potassium in normal subjects and in those with untreated essential hypertension were similar. Older patients with hypertension (>49 yrs) do tend to have raised body sodium which positively correlated with their blood pressure while younger patients (<36 yrs) have reduced body sodium and potassium which correlates inversely with their blood pressure.[16, 17] However, our hypertensive group, of an intermediate age, appeared to have a body composition that was similar to predicted normal for all elements measured. The limited range of values for serum and total body electrolytes in the hypertensive and normal groups compared with the heart failure group reduces the probability of finding significant relations. Chlorine, which is largely present in the extracellular space,[24] did relate to serum concentrations of chloride. Potassium, a largely intracellular electrolyte, and sodium, much of which is present in bone[25] and so not freely exchangeable with the extracellular pool, were poorly related to serum concentrations.

The extracellular fluid volume in our hypertensive patients accorded well with reported figures, and in untreated hypertensive subjects seems to be similar to normal.[33] The numbers with raised concentrations of plasma active renin in this study are too small to analyse the effects of this system on body composition.

HEART FAILURE

The present study clearly shows that total body potassium depletion does occur in patients with heart failure treated with digoxin and diuretics. Others have argued that potassium depletion in such patients is due to cachexia and a loss of protein (nitrogen) mass.[1, 14] Our study demonstrates that this is not the case, and in fact the tendency to higher body calcium and nitrogen suggests that adipose tissue may be preferentially lost in subjects with heart failure, with relative preservation of lean body mass. Indeed the percentage of body weight consisting of fat was lower in elderly subjects with heart failure than in age matched controls.[34] James *et al* have argued that potassium depletion in cachectic patients is due to a loss of cellular nitrogen mass with preservation of collagen nitrogen mass, and that this accounts for the fall in potassium in relation to nitrogen in wasting diseases.[14] They did not, however, specifically study patients with heart failure. Although Burkinshaw and Morgan noted a fall in potassium in relation to nitrogen in heart failure, they too were unable to distinguish between relative changes in collagen and cellular nitrogen because their control groups differed markedly from the study group.[28] Our groups were well matched for height, weight, age, and sex and also had very similar total body nitrogen. If cell mass had been lost nitrogen values were likely to have fallen even if collagen nitrogen mass was preserved. Further support for a true depletion of potassium rather than a change in cellular mass comes from recent evidence that the total body potassium deficit can be corrected without a change in total body nitrogen by use of angiotensin converting enzyme inhibitors, which suppress angiotensin II mediated aldosterone secretion.[13 35] However, amiloride and spironolactone did not correct total body potassium deficits.[36 37]

Others have reported only a poor non-linear relation between serum potassium and total body potassium.[6 38] In our series, where diagnosis was tightly defined and treatment well documented and uniform, we found a good and apparently rectilinear relation between serum and total body potassium over the measured range. Multiple blood sampling may improve this relation. Diurnal variation in potassium concentration[39] is likely to be exaggerated by diuretic treatment. Total body potassium would not be expected to respond in such a rapid manner. Unfortunately multiple samples were not available in hypertensive patients and this may be one reason for the poorer relation observed in those cases.

Diuretic treatment may not be the only explanation for potassium depletion; when patients with high and normal or low plasma active renin concentration were compared, only the former were significantly potassium depleted, though the diuretic dose was very similar in the two groups. After appropriate corrections for nitrogen, however, a small reduction in potassium was detected in the subgroup with low plasma concentrations of active renin. Potassium supplements were also greater in the high renin/low potassium subgroup; this is compatible with the view that potassium supplements are ineffective in correcting diuretic-induced potassium depletion.[2 40] Stimulation of the renin-angiotensin-aldosterone axis will increase renal potassium excretion, but potassium not only stimulates the secretion of aldosterone but also suppresses renin secretion.[41 42] A fall in potassium could then allow a further rise in renin, leading to this inverse relation.

Concentrations of serum bicarbonate were higher in patients with heart failure, as might be expected in the presence of hypokalaemia, but bicarbonate concentrations were similar in normal and high renin subgroups despite significant differences in serum and total body potassium. A long term increase in serum bicarbonate and alkalosis may be less important in the regulation of intra/extracellular potassium ratio in treated heart failure, though it may have a short term regulatory role.

Another feature of interest is the lack of any clear difference in New York Heart Association class, total body sodium, or total body chlorine between subgroups with high or low concentrations of plasma active renin. Where there were statistically insignificant differences they were accounted for by changes in the concentration of the respective electrolytes in the extracellular space. Extracellular fluid volume, even when corrected for weight, was similar in the two groups, suggesting that volume changes are less important in determining renin-angiotensin activity in treated heart failure; however, intravascular volume, which may be important, was not measured. Apart from potassium the only clear differences between high and low renin subgroups were serum concentrations of sodium and mean blood pressure. In heart failure it is likely that these three influences are of prime importance in setting the level of renin-aldosterone-angiotensin activity.[43 44]

Although the heart failure group as a whole had worse renal function, with relatively greater urea than creatinine retention, than the hypertensive group, there were no differences between patients with heart failure in high and low renin subgroups. This suggests that angiotensin II appears not to affect renal function adversely and may well have sustained glomerular filtration and urea excretion in the face of a falling renal blood flow and renal perfusion pressure in our patients.[11 43] Possibly renal function would have been more abnormal in patients with more extreme increases in angiotensin II.[43]

Extracellular fluid volume remained increased in these oedema free patients with heart failure; it is not clear whether further diuretic treatment would have corrected this. Surprisingly, total body oxygen, an index of total body water[23] was reduced in patients with heart failure, suggesting intracellular dehydration. Thus although potassium depletion occurs in heart failure the actual concentration of intracellular potassium may be less abnormal than expected. Total body sodium was 300 mol greater in

300 mol greater in patients with heart failure, and less than half of this difference can be explained by the increase in extracellular fluid volume. The rest could be explained either by an increase in sodium in bone or an increase in intracellular concentrations, because sodium may replace intracellular potassium losses. The alteration in the calcium/phosphorus ratio also suggests a change in bone metabolism, which is not dependent upon the stimulation of renin. Bone calcium was increased by thiazide diuretics,[45] which reduce urinary calcium excretion[46]; however, most of our patients were only on frusemide, which increases urinary calcium excretion. Alternatively the increase in the concentration of bicarbonate may have altered the relation between calcium and phosphorus.

The one year survival of subjects with New York Heart Association grade III heart failure is around 60% and most deaths are sudden—this accords with the frequency of ventricular arrhythmias.[10 47] Potassium depletion may provoke arrhythmias[48] and this effect may be exaggerated by digoxin.[49] Body potassium is largely concentrated in skeletal muscle,[50] which probably acts as a buffer for serum potassium. Depletion of intracellular potassium may lead to much greater short term falls in serum potassium caused by diuretics, changes in pH, or adrenergic activity.[51] Additionally, myocardial potassium concentrations appear to be protected and do not fall when skeletal muscle and serum potassium fall.[52] This could lead to unfavourable changes in transmembrane potential and intramyocardial conduction, further potentiating arrhythmias. If this is so correction of potassium deficits may improve prognosis.

References

1 Morgan DB, Burkinshaw L, Davidson C. Potassium depletion in heart failure and its relation to long-term treatment with diuretics: a review of the literature *Postgrad Med J* 1978;54:72–9.

2 Davidson C, Burkinshaw L, McClachlan MSF, Morgan DB. Effect of long-term diuretic treatment on body potassium in heart disease. *Lancet* 1976;ii:1044–52.

3 Lawson DH, Boddy K, Gray JMB, Mahaffy ME, Mills E. Potassium supplements in patients receiving long-term diuretics for oedema. *Q J Med* 1976;45:469–78.

4 Lye M, Winston B. Whole body potassium and total exchangeable potassium in elderly patients with heart failure. *Br Heart J* 1979;42:568–72.

5 Lye M Body potassium content and capacity of elderly individuals with and without cardiac failure. *Cardiovasc Res* 1982;16:22–5.

6 Flear CTG, Cooke WT, Quinton A. Serum potassium levels as an index of body content *Lancet* 1957; i:458–9.

7 Surveyor I, Hughes D. Discrepancies between whole-body potassium content and exchangeable potassium. *J Lab Clin Med* 1968;71 (part 3):464–71.

8 Boddy K, King PC, Hume R, Weyers E. The relation of total body potassium to height, weight and age in normal adults. *J Clin Pathol* 1972;25:512–7.

9 Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983;51: 831–6.

10 Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy. *Am J Cardiol* 1984;54:147–52.

11 Cleland JGF, Dargie HJ, Hodsman GP, *et al.* Captopril in heart failure: a double blind controlled study. *Br Heart J* 1984;52:530–5.

12 Cleland JGF, Dargie HJ, Ball SG, *et al.* Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. *Br Heart J* 1985;54:305–12.

13 Preston T, Reeds PJ, East BW, Holmes PH. A comparison of body protein in rats by in vivo neutron activation and carcass analysis. *Clin Sci* 1985;68: 349–55.

14 James HM, Dabek JT, Chettle DR, *et al.* Whole body cellular and collagen nitrogen in healthy and wasted man. *Clin Sci* 1985;67:73–82.

15 Williams ED, Boddy K, Brown JJ, *et al.* Whole body elemental composition in patients with essential hypertension. *Eur J Clin Invest* 1982;12:321–5.

16 Lever AF, Beretta-Piccoli C, Brown JJ, *et al.* Sodium and potassium in essential hypertension. *Br Med J* 1981;283:463–8.

17 Beretta-Piccoli C, Davies DL, Boddy K, *et al.* Relation of arterial pressure with body sodium, body potassium and plasma potassium in essential hypertension. *Clin Sci* 1982;63:257–70.

18 Boddy K, King PC, Tothill P, Strong JA. Measurement of total body potassium with a shadow shield whole-body counter: calibration and errors. *Phys Med Biol* 1971;16:275–82.

19 Williams ED, Boddy K, Harvey I, Haywood JK. Calibration and evaluation of a system for total body in vivo activation analysis using 14 MeV neutrons. *Phys Med Biol* 1978;23:405–15.

20 Boddy K, Williams ED, Haywood JK, Harvey I, Harris IA. Scanning in vivo activation analysis: methods and medical applications. In: *Nuclear activation techniques in the life sciences 1978*. Vienna: International Atomic Energy Agency, 1979:775–86.

21 Haywood JK, Harris I, Boddy K, Williams ED. A two-way scanning method for total body in vivo neutron activation analysis. *Phys Med Biol* 1978;23:865–75.

22 Boddy K, Elliot A, Robertson I, Mahaffy ME, Holloway I. A high sensitivity dual-detector shadow-field whole-body counter with and "invariant" response for total body in vivo neutron activation analysis. *Phys Med Biol* 1975;20:296–304.

23 Williams ED, Boddy K. Measurement of whole-body oxygen in living humans by neutron activation analysis. *Int J Appl Rad Isot* 1978;**29**:281–3.

24 Ellis KJ, Vaswani A, Zanzi I, Cohn SH. Total body sodium and chlorine in normal adults. *Metabolism* 1976;**25**:645–54.

25 Ellis KJ, Cohn SH. Correlation between skeletal calcium mass and muscle mass in man. *J Appl Physiol* 1975;**38**:455–60.

26 Skrabal F, Arnot RN, Joplin GF. Equations for the prediction of normal values for exchangeable sodium, exchangeable potassium, extracellular fluid volume, and total body water. *Br Med J* 1973;**ii**:37–8.

27 Yasumura S, Cohn SH, Ellis KJ. Measurement of extracellular space by total body neutron activation. *Am J Physiol* 1983;**244**:R36–40.

28 Burkinshaw L, Morgan DB. Mass and composition of the fat-free tissues of patients with weight-loss. *Clin Sci* 1985;**68**:455–62.

29 Ball SG, Tree M, Morton JJ, Inglis GC, Fraser R. Circulating dopamine: its effect on the plasma concentrations of catecholamines, renin angiotensin, aldosterone and vasopressin in the conscious dog. *Clin Sci* 1981;**61**:417–22.

30 Millar JA, Leckie BJ, Semple PF, Morton JJ, Sonkodi S, Robertson JIS. Active and inactive renin in human plasma: renal arteriovenous differences and relationships with angiotensin and renin substrates. *Circ Res* 1978;**43**(suppl 1):120–7.

31 Fraser R, Guest S, Young J. Comparison of double isotope derivative and radio-immunological estimation of plasma aldosterone concentration. *Clin Sci Mol Med* 1973;**45**:411–5.

32 Atkinson AB, Morton JJ, Brown JJ, *et al.* Captopril in clinical hypertension. Changes in components of the renin-angiotensin system and in body composition in relation to fall in blood pressure with a note on measurement of angiotensin II during converting enzyme inhibition. *Br Heart J* 1980;**44**:290–6.

33 Schalekamp MA, Lebel M, Beevers DG, Fraser P, Kolsters G, Birkenhager WH. Body fluid volume in low-renin hypertension. *Lancet* 1974;**ii**:310–1.

34 Lye M. Body potassium content and capacity of elderly individuals with and without cardiac failure. *Cardiovasc Res* 1982;**16**:22–5.

35 Cleland JGF, Dargie HJ, East BW, *et al.* Total body and serum electrolyte composition in heart failure: the effects of captopril. *Eur Heart J* 1985;**6**:681–8.

36 Davidson C, Gillebrad IM. Use of amiloride as a potassium conserving agent in severe cardiac disease. *Br Heart J* 1973;**35**:456–61.

37 Davidson C, Burkinshaw L, Morgan DB. The effect of potassium supplements, spironolactone or amiloride on the potassium status of patients with heart failure. *Postgrad Med J* 1978;**54**:405–9.

38 Moore FD, Edelman IS, Olney JM, James AH, Brooks L, Wilson GM. Body sodium and potassium: III. Inter-related trends in alimentary, renal and cardiovascular disease, lack of correlation between body stores and plasma concentration. *Metabolism* 1954;**3**:330–50.

39 Ede MCM, Brennan MF, Ball MR. Circadian variation of intercompartmental potassium fluxes in man. *J Appl Physiol* 1975;**38**:163–70.

40 MacLennan WJ, Lye MDW, May T. The effect of potassium supplements on total body potassium levels in the elderly. *Age Ageing* 1977;**6**:46–50.

41 Sealey JE, Kirsham JD, Laragh JH. Natriuretic activity in plasma and urine of salt-loaded man and sheep. *J Clin Invest* 1969;**48**:2210–7.

42 Oparil S, Haber E. The renin-angiotensin system. *N Engl J Med* 1974;**291**:389–94.

43 Brown JJ, Davies JL, Hohnson VW, Lever AF. Robertson JIS. Renin relationships in congestive cardiac failure, treated and untreated. *Am Heart J* 1970;**80**:329–42.

44 Levine TB, Franciosa JA, Vrobel T, Cohn JN. Hyponatraemia as a marker for high renin heart failure. *Br Heart J* 1982;**47**:161–6.

45 Wasnich RD, Benfante RJ, Yano K, Heilburn L, Vogel JM. Thiazide effect on the mineral content of bone. *N Engl J Med* 1983;**309**:344–7.

46 Brickman AS, Massry SG, Coburn JW. Changes in serum and urinary calcium during treatment with hydrochlorothiazide: studies on mechanisms. *J Clin Invest* 1972;**51**:945–53.

47 Meinertz T, Hofman T, Kasper W, *et al.* Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1984;**53**:902–7.

48 Holland OB, Nixon JD, Kuhnert L. Diuretic induced ventricular ectopic activity. *Am J Med* 1981;**70**:762–8.

49 Steiness E, Olesen KH. Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy. *Br Heart J* 1976;**38**:167–72.

50 Knochel JP. Rhabdomyolysis and effects of potassium deficiency on muscle structure and function. *Cardiovasc Med* 1978;**3**:247–61.

51 Struthers AD, Reid JL. The role of adrenal medullary catecholamines in potassium homeostasis. *Clin Sci* 1984;**66**:377–82.

52 Knochel JP, Foley FD, Lipscomb K. High resting cardiac output with exercise-induced pulmonary oedema in the conscious, potassium-deficient dog. *Mineral Electrolyte Metabolism* 1978;**1**:336–44.

Br Heart J 1987;58:239–44

The morphology of the right ventricular outflow tract after percutaneous pulmonary valvotomy: long term follow up

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SUMMARY Twenty nine patients (19 male, mean (SD) age 6·25 (0·5) years (range 0·16–15 years))with typical pulmonary valve stenosis were treated by balloon dilatation of the pulmonary valve. They were studied by echocardiography before the procedure, immediately after it, and at follow up (mean (SD) 10·2 (5·6) months, n=18). The morphology of the pulmonary valve, the right ventricular-pulmonary artery gradient, and ratio of the systolic to diastolic endocardial dimensions (infundibular ratio) were examined. No patient had pulmonary regurgitation before the study. The valve gradient was significantly reduced (47%) from a mean (SD) of 72 (31) to 37 (23) mm Hg with no short term change in cardiac index after dilatation with a balloon with a mean (SD) diameter that was 118 (10·8)% of the valve annulus. The infundibular ratio was unchanged by the procedure (0·49 (0·11) (n = 21) before dilatation and 0·47 (0·14) (n = 16) after dilatation). In twenty seven patients the commissure of the pulmonary valve was seen to be torn after dilatation. Two patients with bicuspid valves had flail leaflets. Doppler examination at follow up showed mild pulmonary insufficiency in all 29 patients; the mean (SD) valve gradient (31 (±21) mm Hg) at follow up was no different from the gradient found immediately after the procedure and infundibular ratio (0·58 (0·15) was not abnormal.

These data indicate that commissural tears are the primary mechanism of valve disruption and demonstrate that the dynamic right ventricular outflow tract obstruction relaxes and gradient reduction persists at follow up.

Percutaneous pulmonary valvotomy was first described by Rubio and Limon-Lason in 1954. They used a wire loop technique,[1 2] but recently Semb *et al* and Kan *et al* have used balloon tipped catheters[3 4] for the procedure, which has become established as a non-surgical treatment for congenital pulmonary valve stenosis.[5–8] Some patients, however, have haemodynamically important obstruction of the right ventricular outflow tract after valvotomy[5–8] despite what appears to be a tear in the pulmonary valve.[9] We have studied this obstruction in patients after percutaneous pulmonary valvotomy.

Patients and methods

Over a 28 month period from January 1984, 38 percutaneous pulmonary valvotomies were performed for isolated pulmonary valve stenosis in 36 patients (19 boys; mean (SD) age 6·25 (0·5) years). Seven patients had clinical and echocardiographic evidence of dysplasia of the pulmonary valve and were excluded from the analysis.[10] All patients had clin-

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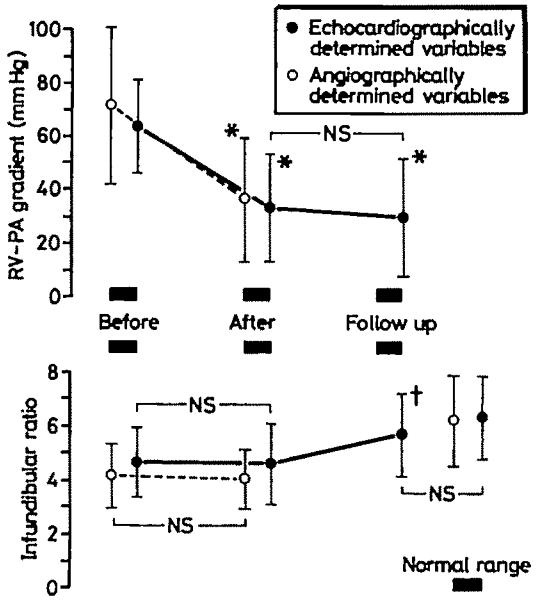

Fig 1 *Right ventricular to pulmonary artery (RV–PA) gradient and infundibular ratio before, immediately after, and at follow up after balloon dilatation.* **$p < 0{\cdot}001$ compared with values before valvotomy;*† *$p < 0{\cdot}02$ for comparison of values immediately after valvotomy with values at follow up.*

ical evidence of moderate to severe pulmonary valve stenosis[11] (fig 1). Informed consent was obtained from all parents as outlined and approved by the Human Subjects Protection Committee of the Faculty of Medicine, The Hospital for Sick Children, and University of Toronto.

Cross sectional echocardiography and Doppler echocardiography were performed in all patients before the procedure and within 24 hours of valvotomy. We used 3·0, 5·0, or 7·5 MHz mechanical sector scanners on either an ATL 600, Ultramark 8 (Advanced Technology Laboratories Inc., Bellevue, WA), or Hewlett-Packard (Model 77020A) ultrasound imaging systems fitted with pulsed or continuous wave Doppler probes. Standard and high parasternal short axis views were routinely used to image the pulmonary valve, annulus, and infundibulum.[9] Pulmonary annulus diameters measured at the hinge points of the pulmonary valve annulus were obtained from echocardiographic images (short axis view) and compared with the lateral projection from the right ventriculogram obtained before valvotomy. Doppler estimates of pulmonary valve gradients were obtained by use of the Bernoulli relation.[12] Doppler estimated right ventricular outflow tract gradients in our laboratory were compared with simultaneous intracardiac pressures (right ventricle–pulmonary artery). This gave a correlation of $r = 0{\cdot}95$; RV–PA gradient (cath) = 0·89 RV–PA gradient (Doppler) + 3·98; SEE = 8·5, $n = 29$.

Cardiac catheterisation was performed under ketamine anaesthesia given by continuous infusion.[13] The details of the dilatation procedure used in our laboratories have been outlined elsewhere.[14] Briefly, two venous catheters (7 French) were manoeuvred into the right ventricle and main pulmonary artery for simultaneous gradient measurements, and a femoral artery line (5 French) was placed to monitor systemic pressure. Cardiac output was measured by a Fick determination (measured oxygen consumption), thermodilution, or dye curve, and a biplane right ventricular axial angiogram (one plane always true lateral) was performed. A Teflon coated exchange guide wire was positioned, preferably in the distal left pulmonary artery, and a balloon tipped 3 cm long 8 or 9 French valvotomy catheter (Mansfield Scientific, Waterstown, MA) was passed over it and across the pulmonary valve annulus. The approximate location of the valve was determined from the lateral right ventriculogram and marked by a radio-opaque marker taped to the lateral chest wall. We selected balloon catheters that were approximately 120% of the diameter of the pulmonary valve annulus measured on the lateral right ventriculogram and corrected for magnification against the angiocatheter diameter. Several balloon inflation/deflation cycles (average 4) lasting approximately 15–20 seconds each were performed until no discernible waist (caused by the stenotic pulmonary valve leaflets) was seen during fluoroscopy. Inflation pressures were initially measured by an in-line manometer to the rated manufacturer's tolerance (3–4 atm) (30·32–40·43 kPa) but this was abandoned in the later 25 patients because maximal intraballoon pressures were rarely achieved.[7] Right ventricular and femoral artery pressures were monitored throughout the dilatation procedure. Right ventricular-pulmonary artery pressures were measured immediately upon withdrawal of the balloon catheter and were observed for 15 to 20 minutes before cardiac output measurements and biplane right ventricular axial angiography were repeated.

From a replay of the right ventriculogram we determined whether the right ventricular outflow tract showed dynamic or fixed obstruction. A dynamic obstruction was measured in terms of the infundibular ratio. This was calculated as the ratio of the systolic and diastolic endocardial dimensions measured at a point equidistant from the pulmonary and tricuspid valves. Ten normal right ventricular angiograms were similarly measured and found to have a mean (SD) ratio of 0·64 (0·16). Additionally, an echocardiographically determined infundibular ratio was measured before cardiac catheterisation from the short axis view at the base of the heart between pulmonary and tricuspid valves at end systole and diastole. The infundibular ratio in 10 patients with normal cardiac anatomy was 0·63 (0·16). Angiograms complicated by extrasystoles or echocardiograms of poor resolution were not used in data analysis.

Two patients required a second intracardiac study and valvotomy at 9 and 16 months because haemodynamically important right ventricular outflow tract obstruction recurred. Two other patients needed subsequent surgical repair because of fixed fibromuscular and subpulmonary obstruction and both required an outflow tract patch; one of these patients has been reported in detail elsewhere.[9] A third patient with fixed obstruction is awaiting surgical repair. One patient had undergone a surgical pulmonary valvotomy three months before balloon dilatation of the valve.

STATISTICAL ANALYSIS

Data are presented as mean (1 SD). Statistical significance was determined by the two tailed *t* test for paired data. Individual patient data are available from the authors upon request.

Results

ECHOCARDIOGRAPHIC DATA BEFORE BALLOON DILATATION

In all but two patients commissural fusion of a tricuspid pulmonary valve was identified as the mechanism of stenosis[15] (fig 1). Doppler study did not show evidence of pulmonary regurgitation in any patient. The echocardiogram predicted the angiographic pulmonary annulus as: angiographic annulus (mm) = 1·04 (echographic annulus (mm)) − 1·03; r = 0·87; SEE = 1·1; n = 20. The mean (SD) pulmonary valve gradient in the unsedated resting patients before catheterisation was 66·1 (16·7) (range 39 to 100 mm Hg).

RESULTS IMMEDIATELY BEFORE AND IMMEDIATELY AFTER VALVOTOMY

The mean (1 SD) pulmonary valve annulus was 14·7 (3·3 mm) (range 8 to 20 mm) by angiography. The average right ventricular–pulmonary artery gradient fell by 47% at catheterisation from 72 (31) mm Hg (range 34–172 mm Hg) to 37 (23) mm Hg (range 5 to 114 mm Hg) (p < 0·001) (fig 1). Similarly, the ratio of right ventricular pressure to systemic arterial pressure fell by 59% from 0·85 (0·26)% (range 0·47 to 1·51%) to 0·50 (0·25)% (range 0·16 to 1·30%). The pulmonary valves were dilated with balloons that were on average 17·5 (3·4) mm in diameter and 118 (10·8)% of the annulus size. There was no change in the angiographically measured size of the annulus after dilatation. Mean cardiac index was 3·98 (1·06) l/min/m^2 and there was no significant change after dilatation (4·29 (1·21) l/min/m^2, n = 12). The infundibular ratio was measured by angiography (0·42 (0·11), n = 30) and echocardiography (0·49 (0·11), n = 21) before dilatation. There was no significant difference in either (0·41 (0·1), n = 30; and 0·47 (0·14), n = 16 respectively) after dilatation. After catheterisation, when the child was unsedated and resting, the echocardiographic pulmonary valve gradient was 53% lower (34 (18) mm Hg) (range 8 to 80, n = 27) than before the procedure (p < 0·001) (fig 1).

In all patients there was a dynamic infundibular component to the right ventricular obstruction as shown by the replay of the lateral right ventricular angiogram, and in three patients there was a fixed obstructive element. We identified commissural tears in all patients who had trileaflet valves shown by cross sectional echocardiography. Tears were seen in one or two commissures and occasionally extended to the margin of the valve annulus (fig 2). In the two patients with bicuspid valves the valve leaflet tissue was ruptured and in both there was a non-competent flailed valve.

LONG TERM FOLLOW UP

Echocardiographic images of the right ventricular outflow tract and pulmonary valve and Doppler estimates of the pulmonary valve gradients were obtained at follow up in 18 patients, 10·2 (5·6) (range 4 to 24) months after the initial procedure. The average valve gradient was (31 (21) mm Hg) not significantly different from the value immediately after dilatation. Additionally the echocardiographically derived infundibular ratio (0·5 (0·15)) was not significantly different from the normal values (fig 1). All but four patients had Doppler evidence of pulmonary insufficiency of mild degree; no patients showed progression of the insufficiency either by Doppler study or by clinical evaluation.

At the end of the procedure nine (31%) of 29 patients had right ventricular pressures that were > 50% of systolic or a gradient of > 35 mm Hg. In three of these subpulmonary obstruction established by echocardiography and angiography was unchanged at follow up, suggesting a fixed component. In four patients there had been a further reduction in valve gradient to 24 (6·6) mm Hg and an increase in infundibular ratio from 0·39 (0·18) to 0·54 (0·16) (p < 0·0001). In one patient the valve gradient was unchanged (36 mm Hg); another has not yet been seen at follow up.

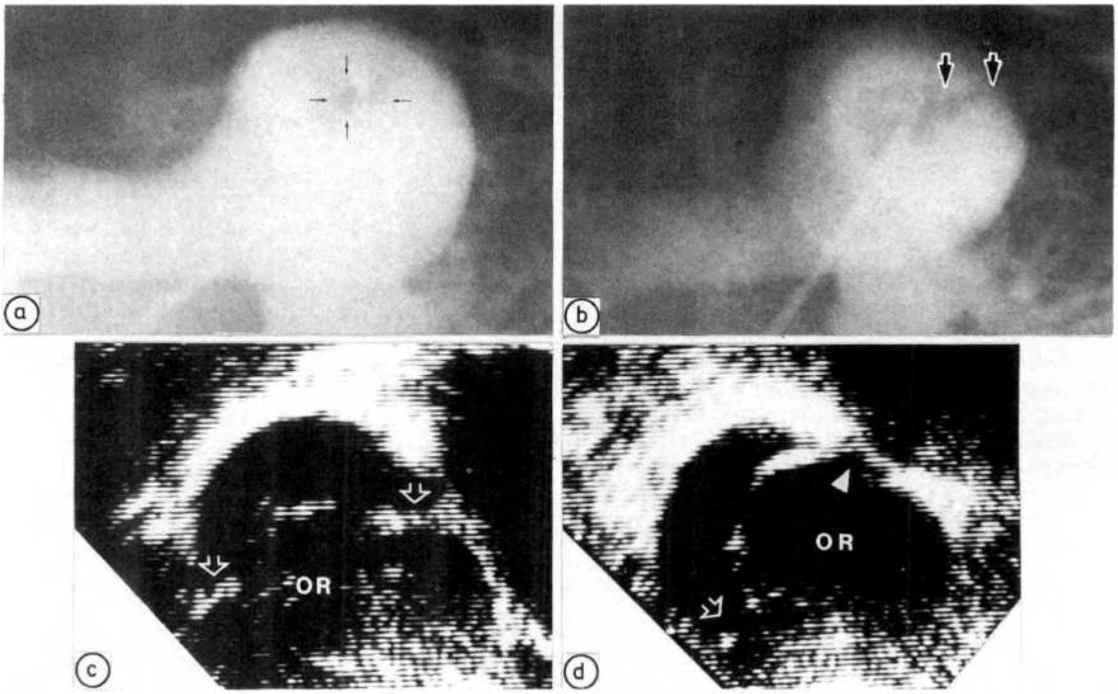

Fig 2 *Pulmonary artery angiograms: (a) before dilatation (cranial-caudal view) showing outlining of the haemodynamic orifice with non-opacified blood (arrows); (b) after dilatation showing a linear tear to the annulus margin (arrows) outlined by non-opacified blood. (c) Short axis, high parasternal echocardiogram before dilatation showing tricuspid valve and two of the fused commissures at 3 and 7 o'clock (arrows). (d) Echocardiogram after dilatation showing the split (solid arrow). The other commissure at 7 o'clock remains fused. OR, orifice*

Two patients had a second valvotomy with balloons that were 115% of the valve ring diameter. In one the gradient fell from 54 to 18 mm Hg and this fall was maintained at six month follow up. In the second child, however, the gradient at follow up was unchanged (81 mm Hg) and there was angiographic and echocardiographic evidence of subvalvar obstruction that did not resolve over a 12 month period. This child had surgical repair with an infundibular patch and surgical valvotomy. The valve leaflets were bicuspid and markedly thickened with a 9 mm orifice and fused commissures. There was no evidence of valve disruption caused by balloon dilatation.

Discussion

Balloon dilatation of the pulmonary valve was reported to be a safe and effective means of reducing the right ventricular to pulmonary artery gradient in typical pulmonary valve stenosis.[4–8] Our experience with this technique further supports these initial observations. The mechanism of stenosis in this setting appears to be varying degrees of commissural fusion on a trileaflet valve with minimal or no thickening of valve leaflets.[15] Echocardiographic data and the appearance at operation show that in most cases the reduction in gradient was apparently achieved by splitting of adherent commissural elements (fig 2).[8 9 16] Pulmonary valve insufficiency that is demonstrable by echocardiography and Doppler examination is an inevitable consequence of an effective dilatation. Insufficiency is occasionally audible by auscultation,[9 17 18] suggesting damage to the leaflet-supporting apparatus. It is not clear, however, why pulmonary insufficiency is a component of an effective dilatation. Commissural tearing was never seen to be uniform in all three margins and sometimes extended to the limits of the valve annulus. Thus loss of support at the commissural marginal tear may account for the insufficiency.

Paracommissural tears along leaflet tissue could also produce echocardiographic findings that are indistinguishable from those produced by commissural splitting.[7] Annular measurements after balloon valvotomy discount the notion that ring dilatation (by overlarge balloons) may contribute to this finding. At follow up most patients continued to have valve insufficiency; this was mild and did not increase to become a clinical problem. These incomplete tears probably also account for the residual gradients seen after dilatation. The asymmetry of the tears may also account for the improved results in gradient reduction seen when balloons that have larger diameters than the valve annulus are used.[4 19]

Angiographic examination after dilatation in most patients demonstrated improved valve leaflet mobility of only a single leaflet, with the continued presence of a "contrast jet", albeit wider than before the procedure, and doming of the adjacent leaflets implying persistence of fusion of the valve commissures (P Burrows, personal communication). Two of our patients had bicuspid valves and in these patients balloon valvotomy resulted in flail, non-supported valve mechanisms and regurgitation as previously reported by Lababidi and Wu.[5] We can only speculate about the reasons for this finding. There may be an intrinsic abnormality in the valve-annulus attachments or perhaps a bicuspid valve is more vulnerable to stress, because the area of the valve leaflet is larger. Alternatively, the action of the heart on the balloon may result in a shearing motion that disrupts the valve attachments to the ring. All these elements could be operating to varying degrees.

The data from our series suggest that a dynamic obstruction of the subpulmonary outflow tract is a frequent component of pulmonary valve stenosis. This may persist after the procedure[7 17] but if valve dilatation is successful it can be expected to regress[18] with a further reduction in gradient. This observation is supported by previous studies after surgical valvotomy.[19-21] Unlike Ben-Shacher *et al* we did not find that dynamic obstruction of the outflow tract became worse after the procedure,[16] despite the fact that before dilatation 11 of our patients had right ventricular pressures > 85% systemic; in five right ventricular pressure was greater than systemic pressure. It may be that our results were influenced by the use of continuous ketamine anaesthesia rather than sedation during the procedure. A reduction of sympathetic outflow could have moderated the effect of the hypercontractile outflow tract.

When the residual gradient is > 35 mm Hg or 50% systemic right ventricular pressures we use cross sectional echocardiography to visualise the morphology of the valve (to assess whether a leaflet tear has occurred) and we carefully examine the right ventriculogram obtained after balloon valvotomy, paying particular attention to the mobility of the valve leaflets. We do not perform further dilatations with larger balloons if the above studies suggest that the commissural tear is adequate. In such circumstances it is likely that the gradient will be further reduced as infundibular hypertrophy regresses.

References

1 Rubio Y, Limon-Lason R. Treatment of pulmonary valvular stenosis and of tricuspid stenosis using a modified catheter. Proceedings of the 2nd World Congress of Cardiology, Washington DC, September 1954, page 205.

2 Rashkind WJ. Interventional cardiac catheterization in congenital heart disease. *Int J Cardiol* 1985;7:7–11.

3 Semb BKH, Tjonneland D, Stake G, Aabyholm G. "Balloon valvulotomy" of congenital pulmonary valve stenosis with tricuspid valve insufficiency. *Cardiovasc Radiol* 1979;2:239–41.

4 Kan JS, White RI Jr, Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary valve stenosis. *N Engl J Med* 1982;307;540–2.

5 Lababidi Z, Wu J-R. Percutaneous balloon pulmonary valvuloplasty. *Am J Cardiol* 1983;52:560–2.

6 Kan JS, White RI Jr, Mitchell SE, Anderson JH, Gardner TJ. Percutaneous transluminal balloon valvuloplasty for pulmonary valve stenosis. *Circulation* 1984;69:554–60.

7 Rocchini AP, Kveselis DA, Crowley D, Dick M, Rosenthal A. Percutaneous balloon valvuloplasty for treatment of congenital pulmonary valvular stenosis in children. *J Am Coll Cardiol* 1984;3:1005–12.

8 Tynan M, Baker EJ, Rohmer J. Percutaneous balloon pulmonary valvuloplasty. *Br Heart J* 1985;53:520–4.

9 Benson LN, Smallhorn J, Freedom RM, Trusler GA, Rowe RD. Pulmonary valve morphology after balloon dilation of pulmonary valve stenosis. *Cathet Cardiovasc Diagn* 1985;11:161–6.

10 Musewe NN, Robertson MA, Benson LN, *et al.* The dysplastic pulmonary valve: echocardiographic features and results of balloon dilatation. *Br Heart J* 1987;57:364–70.

11 Rowe RD. Pulmonary stenosis with normal aortic root. In: Keith JD, Rowe RD, Vlad P, eds. *Heart diseases in infancy and childhood.* New York: MacMillan, 1978: 761.

12 Hatle L, Anglesen B. *Doppler ultrasound in cardiology.* Philadelphia: Lea and Febiger, 1969: 8–73.

13 Shulman D, Beardsmore CS, Aronson HB, Godfrey S. The effects of ketamine on the functional residual capacity in young children. *Anesthesiology* 1985;62:551–6.

14 Freedom RM, Smallhorn JF, Benson LN. Evaluation of severity of pulmonary stenosis and results of pulmonary valve balloon angioplasty in children. Proceedings from St. Christopher's Symposium in Management of Congenital Valve Disease (in press), 1987.

15 Jeffrey RF, Moller JH, Amplatz K. The dysplastic pulmonary valve: a new roentgenographic entity. *Am J Roentgenol Radium Ther Nucl Med* 1972;114:322–39.

16 Ben-Shachar G, Cohen MH, Sivakoff MC, Portman MA, Riemenbschneider TA, Van Hee Keren DW. Development of infundibular obstruction after per-

cutaneous pulmonary balloon valvuloplasty. *J Am Coll Cardiol* 1985;5:754–6.

17 Radtke W, Keane JF, Fellows KE, Lang P, Lock JE. Percutaneous balloon valvotomy of congenital pulmonary stenosis using oversized balloons. *J Am Coll Cardiol* 1986;8:909–15.

18 Kveselis DA, Rocchini AP, Snider R, Rosenthal A, Crowley DC, Dick M II. Results of balloon valvuloplasty in the treatment of congenital valvular pulmonary stenosis in children. *Am J Cardiol* 1985;56:527–32.

19 Engel MA, Holswade GR, Goldberg HP, Lukas DS, Glenn F. Regression after open valvotomy of infundibular stenosis accompanying severe valvular pulmonic stenosis. *Circulation* 1958;17:862–73.

20 Griffith BP, Hardesty, RL, Skewers RD, Lenberg DB, Ferson PF, Bahnson HT. Pulmonary valvotomy done for pulmonary stenosis: results in children with and without muscular infundibular hypertrophy. *J Thorac Cardiovasc Surg* 1982;83:577–83.

21 Ring JC, Kulik TJ, Burke BA, Lock JE. Pathologic changes induced by dilatation of the pulmonary valve annulus with over-large balloons in normal newborn lambs. *Am J Cardiol* 1985;55:210–4.

Br Heart J 1987;58:245–50

Transvenous cardioversion for the management of recurrent ventricular arrhythmias

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SUMMARY The efficacy of transvenous cardioversion and defibrillation for treating life threatening spontaneous ventricular arrhythmias was assessed in a study of 17 patients in a cardiac care unit. Eleven had ventricular tachycardia, five had ventricular fibrillation, and one had both. Transvenous cardioversion successfully terminated tachyarrhythmias on 42 separate occasions in ten patients. Stable electrode positions could not be achieved in two patients, recurrent late displacement occurred in one, and four patients had no further arrhythmias requiring cardioversion once the lead was placed. The energy levels required for successful cardioversion ranged from 0·05 J to 25 J for ventricular tachycardia and from 1 J to 25 J for ventricular fibrillation. The nine successful shocks of 1 J or less did not require sedation or general anaesthesia. High energy (25 J) endocardial shocks were unsuccessful in terminating arrhythmias in two patients, one with ventricular tachycardia and the other with both ventricular tachycardia and fibrillation. Minor unwanted effects of endocardial shocks occurred in five patients. These were acceleration of ventricular tachycardia in two patients and complications of pacing via the special lead in three others: failure of sensing occurred in all three and one patient also had a transient rise in pacing threshold. A postmortem examination in one patient who had received three unsuccessful high energy shocks revealed localised endocardial necrosis at the site of the distal electrode.

Transvenous cardioversion offers advantages over external cardioversion but at present practical difficulties limit its application to patients with recurrent ventricular arrhythmias that cannot readily be controlled by conventional methods.

Electrical treatment of life threatening ventricular arrhythmias occurring after myocardial infarction poses several problems; these include the need for repeated general anaesthetics, delays before cardioversion, and superficial burns. Nevertheless, the long term prognosis can be good in those patients who survive the unstable acute phase. Although low energy endocardial shocks have been shown to terminate ventricular arrhythmias induced during electrophysiological testing,[1-3] little experience of the use of transvenous cardioversion with an external unit has been reported for spontaneous ventricular arrhythmias.[2 4] We have tested the applicability of this technique to patients in a cardiac care unit.

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Patients and methods

We studied 11 men and six women (aged 46–75 years) with recurrent ventricular arrhythmias; eleven had recurrent ventricular tachycardia, five had recurrent ventricular fibrillation, and one had both. All but one patient had sustained a recent acute myocardial infarction. One patient was treated for malignant postoperative ventricular arrhythmias. A median of four attacks (2–30) of a ventricular arrhythmia occurred before transvenous cardioversion was attempted. All patients had been treated with antiarrhythmic drugs in the cardiac care unit of the Royal Sussex County Hospital, Brighton or King's College Hospital, London. Table 1 summarises the patient data.

The temporary pacing lead (Medtronic 6880, Medtronic Inc, Minneapolis, USA) designed for

Table 1 *Patient details*

Patient No	*Age*	*Sex*	*Clinical diagnosis*	*Recurrent arrhythmia*	*No of episodes*	*Previous drug treatment*
1	53	F	MI	VF	5	L, Am
2	69	F	Hysterectomy	VF	3	L
3	72	M	MI	VF	6	L
4	59	M	MI	VF	4	L, Am, Fl
5	74	M	MI	VF	3	L, Am
6	76	M	MI	VF/VT	4	L, Am, Fl, P
7	72	M	MI	VT	3	L, Fl
8	67	M	MI	VT	3	L, Am, M
9	46	F	MI	VT	4	A, M
10	61	F	MI	VT	3	L, P
11	63	M	MI	VT	5	M, Am, Fl
12	69	F	MI	VT	30*	L, Am, Fl, M
13	60	M	MI	VT	11	L, Am, Fl, P
14	61	M	MI	VT	3	L, Am
15	57	M	MI	VT	3	L
16	59	M	MI	VT	4	L, Am, P
17	75	F	MI	VT	2	L
Mean	64	11M/6F				2·3 drugs per patient
Median					4	

*28 of the 30 shocks were given in Lewisham Hospital.
Am, amiodarone; Fl, flecainide, L, lignocaine; M, mexiletine; MI, myocardial infarction; P, procainamide; VF, ventricular fibrillation, VT, ventricular tachycardia.

transvenous cardioversion has bipolar pairs of stainless steel electrodes—at the tip in the right ventricular apex and 13 cm proximally to lie near the junction of the right atrium and superior vena cava. The electrodes in each pair are separated by 5 mm and have a combined surface area of 125 mm^2. When the shock is delivered the two distal electrodes are coupled together to form the cathode and the two proximal electrodes to form the anode. The distal pair is used for sensing to synchronise cardioversion, and can also provide bipolar pacing. The lead was introduced through a 10·5 French gauge split sheath introducer into a subclavian vein in 13 patients and in the remaining four patients via an antecubital vein or an external jugular vein. We used a central stylet to manipulate the lead in a manner similar to that used for permanent pacing.

The cardioverter defibrillator used in this study was a purpose built manually operated device (Medtronic 5350, Medtronic Inc., Minneapolis, USA) that delivers a truncated exponential waveform. The waveform is described in terms of the relation of the voltage of the trailing edge to the leading edge. This is called "tilt" (fig 1). The percentage tilt is the percentage decrease between the leading edge and the trailing edge voltage. Three different tilts were available, namely, 27%, 63%, or 82%. The shocks used throughout the study had 63% tilt

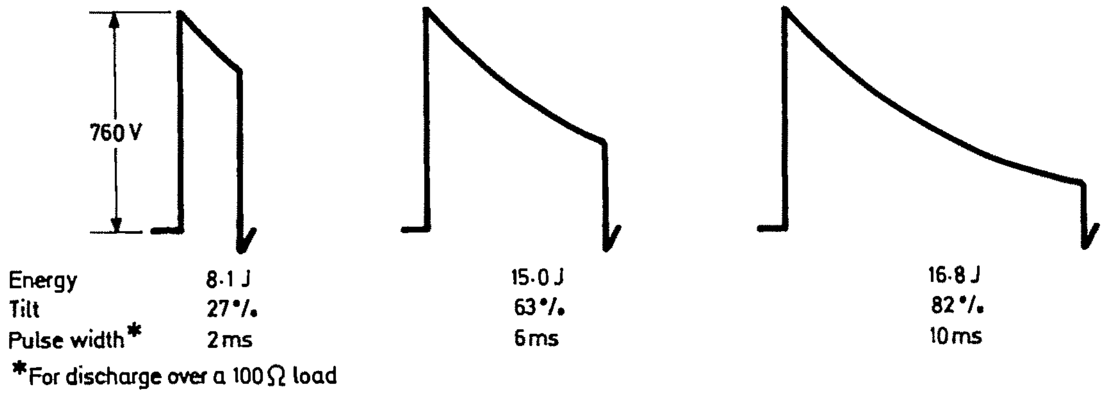

Fig 1 *The leading edge voltage for all three waveforms shown above is 760 V. The percentage tilt refers to the percentage decrease between the leading edge and the trailing edge voltage.*

Table 2 *Energy levels used for transvenous cardioversion*

	Attempt											
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Energy (J)	0·05	0·10	0·25	0·50	1·00	1·50	2·0	5·0	10·0	15·0	20·0	25·0
Leading edge voltage (V)	44	60	98	132	193	236	271	436	610	747	686	971

Tilt of 63% and pulse width of 6 ms used throughout.

and lasted six seconds. An energy level of 0·05 J was used for the first attempt at cardioversion and this was increased by 11 steps until success was achieved or a maximum output of 25 J had been used (table 2). If an arrhythmia recurred, the energy level chosen for the next attempt at cardioversion was set at one step lower than that used in the previous successful cardioversion. In patients with ventricular tachycardia discharge delivery was synchronised by means of the apical right ventricular electrogram. The charging time for the cardioverter defibrillator was less than 10 seconds even for high energy shocks. Sedation or general anaesthesia was used if shocks caused appreciable discomfort.

When necessary, ventricular pacing could be provided by connecting an external pulse generator to the cardioverter defibrillator. Simultaneous defibrillation and pacing was prevented by a switch that allowed choice between pacing, synchronised shock, or asynchronous shock.

Results

In 14 of the 17 patients the pacing lead was positioned successfully and remained stable. Of these 14, 10 had further tachycardia that required cardioversion; all were successfully treated at least once. Three had ventricular fibrillation, six had ventricular tachycardia, and one patient had both. Tachycardia was terminated on 42 separate occasions. Figure 2 shows an example of successful transvenous cardioversion.

Four patients in whom the lead remained stable did not receive endocardial shocks. Three settled on antiarrhythmic treatment once the lead was in position, while one patient developed self-terminating multiform ventricular tachycardia that was suppressed successfully by ventricular overdrive pacing via the special lead. In the three remaining patients difficulties were experienced with lead placement or subsequent lead stability: in one, ventricular fibrillation was triggered repeatedly on crossing the tricuspid valve; in the second, instability prevented initial lead placement; in the third, the procedure was abandoned because of repeated lead displacement.

The energy levels associated with successful cardioversion varied from 0·05 J to 25 J (median 10 J). Ventricular tachycardia was terminated by synchronised shocks of 0·05 J–25 J (median 2 J) and ventricular fibrillation by asynchronous shocks ranging from 1 J to 25 J (median 10 J). The difference between the mean energy levels required for cardioversion of tachycardia and fibrillation did not reach statistical significance. Perception of discomfort caused by transvenous cardioversion varied, but the nine successful shocks of 1 J or less did not cause undue discomfort and required neither sedation nor general anaesthesia.

Transvenous cardioversion failed to terminate some episodes of ventricular arrhythmias in two patients. High energy (25 J) endocardial shocks were unsuccessful in terminating ventricular tachycardia in one patient and ventricular tachycardia or fibrillation in another; sinus rhythm was restored in each case by external countershock. In both of these patients further arrhythmias did respond to transvenous cardioversion. Subsequently these two patients died of intractable cardiac failure. Necropsy in one who had received three unsuccessful high energy shocks revealed an area of myocardial necrosis to a depth of 0·5 cm around the distal tip of the lead.

Unwanted effects of transvenous cardioversion occurred in five patients. Two of them had acceleration of ventricular tachycardia or provocation of ventricular fibrillation in response to synchronised low energy shocks (fig 3). Reversion to sinus rhythm was achieved by higher energy endocardial shock and by external countershock. The unwanted effects of transvenous cardioversion in the three other patients were related to pacing after endocardial shock. Although pacing was achieved satisfactorily in most patients who required it, inappropriate pacing due to failure of sensing after endocardial shock occurred in each of these three patients. In addition, one had a transient rise in pacing threshold from 0·7 V to 2·4 V.

Table 3 summarises the clinical outcome of all the patients. After the acute phase had settled, the tachycardia in nine of the 17 patients was suppressed by antiarrhythmic drugs, two underwent left ven-

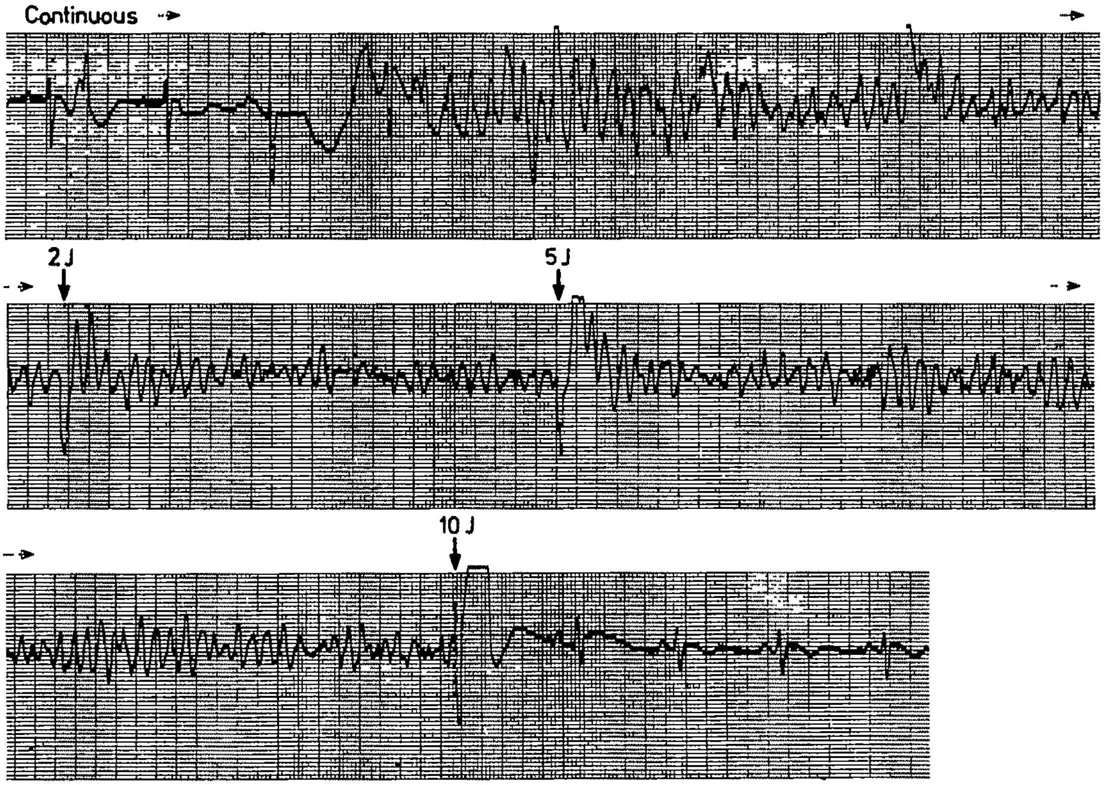

Fig 2 *Successful transvenous cardioversion (10 J) in a patient with recurrent ventricular fibrillation. A 5 J endocardial shock had been successful before. On this occasion transvenous cardioversion with shocks of 2 J and 5 J was unsuccessful but sinus rhythm was restored after a 10 J shock.*

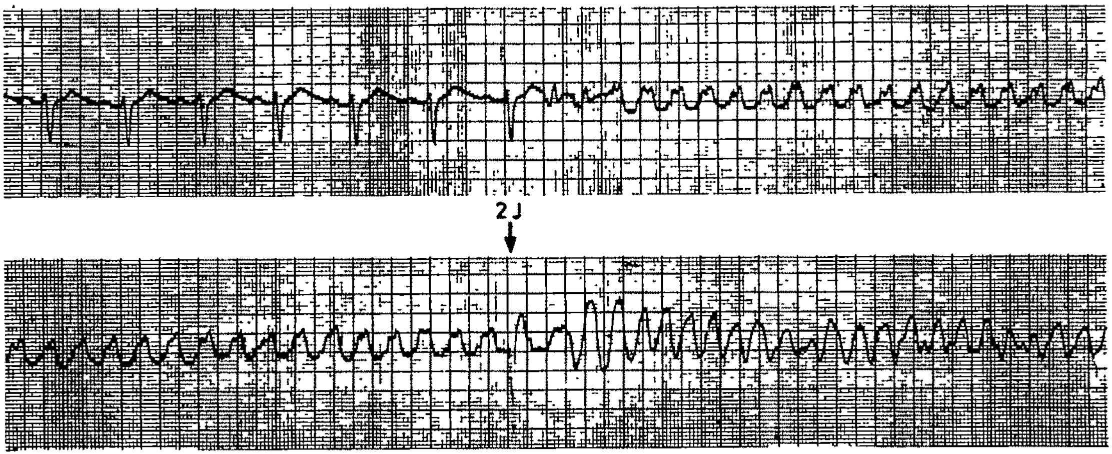

Fig 3 *Provocation of ventricular fibrillation by a synchronised low energy shock. The top panel shows the onset of ventricular tachycardia. In the lower panel treatment of this ventricular tachycardia by a synchronised endocardial shock (2 J) provoked the onset of ventricular fibrillation.*

Table 3 *Results and clinical outcome*

Patient No	*Arrhythmia*	*Successful cardioversions*	*Unsuccessful cardioversions*	*Mean energy level*	*Clinical outcome*
1	VF	3	—	6·0	M (Am, D)
2	VF	5	—	11·0	Died
3	VF	2	—	15·0	Died
4	VF	NFA	—	—	Surgery
5	VF	LP	—	—	Died
6	VT/ VF	5 2	F F	18·0 23·0	Died
7	VT	7	—	7·8	M (Fl)
8	VT	3	—	1·5	M (Am) Surgery
9	VT	1	—	0·5	M (Am)
10	VT	2	A	6·0	M (Am)
11	VT	6	A	0·4	M (Pr)
12	VT	6	F	25·0	Died
13	VT	NFA	—	—	M (Am)
14	VT	NFA	—	—	M (Am)
15	VT	LP	—	—	M (Am)
16	VT	LP	—	—	M (Am, Pr)
17	VT	MI	—	—	Pacemaker

A, acceleration of ventricular tachycardia or provocation of ventricular fibrillation, Am, amiodarone; D, disopyramide, F, failed cardioversion (25 J); Fl, flecainide, LP, lead placement problem, M, stabilised on medical treatment, MI, multiform ventricular tachycardia suppressed by overdrive pacing, NFA, no further arrhythmias, Pr, procainamide, VF, ventricular fibrillation, VT, ventricular tachycardia

tricular aneurysmectomy, and one received a permanent pacemaker. The remaining five patients died from intractable cardiac failure.

Discussion

Low energy endocardial shocks (8 mJ to 1 J) were reported in 1982 to be effective in terminating ventricular tachycardia in dogs.[5] Subsequent studies of patients with inducible ventricular tachycardia found that reversion to sinus rhythm using intracavity shocks could be achieved in 60–80% of cases by energy levels of $\leqslant$30 J.[1 3 6] The technique, however, has not yet been fully evaluated. Possible benefits of transvenous cardioversion over conventional external countershock in the treatment of spontaneous recurrent ventricular arrhythmias include a reduction in the delays to cardioversion, less need for general anaesthetics, and no superficial burns. The interval between the onset of arrhythmia and cardioversion was not timed accurately in this study but transvenous cardioversion was associated with little delay provided that the patient was unconscious or responded to a low energy (< 1 J) shock that required no sedation. In conscious patients higher energy endocardial shocks required the intravenous administration of a benzodiazepine and the delay before cardioversion was similar to that for external countershock. No patient required a general anaesthetic.

The present study is one of the largest so far reported of the use of transvenous cardioversion for spontaneous ventricular arrhythmias. In 1982 Yee *et al* reported early experience of using endocardial shocks to treat ventricular tachyarrhythmias in patients in a cardiac care setting.[4] In their report of eight patients, transvenous cardioversion was used successfully to terminate 95% of 91 episodes of ventricular tachycardia, three episodes of ventricular flutter, and four of six episodes of ventricular fibrillation. Other reports of the use of transvenous cardioversion have concentrated upon the treatment of ventricular arrhythmias induced during electrophysiological testing rather than arising spontaneously.[1 2 7]

The energy levels required for successful cardioversion of spontaneous ventricular arrhythmias by endocardial shock varied widely. This variation in a small series would mask any tendency to a difference in the energy levels required for ventricular tachycardia and ventricular fibrillation. In a study of ventricular arrhythmias induced during electrophysiological testing, Waspe *et al* reported that higher energy levels were needed for conversion of ventricular fibrillation (mean 20·4 J) than for most episodes of ventricular tachycardia (mean 1·4 J).[3] Moreover, Perelman *et al* suggested an inverse relation between the threshold for termination and the cycle length of ventricular tachycardia.[8] The evidence from this study does not militate against these findings.

Although transvenous cardioversion was successful for the majority of patients in this study, several important problems were revealed. Difficulties with lead placement and stability precluded the use of this treatment in three of our patients. Modification of the special pacing lead with reduction of the stiffness of the tip of the lead may ease lead placement and improve stability. In addition to problems related to the lead, several unwanted effects occurred as a result of endocardial shocks: acceleration of ventricular tachycardia or provocation of ventricular fibrillation after a synchronised shock has already been reported after transvenous cardioversion[2] and was related to the timing of the discharge within the QRS complex.[5 8] Moreover, the usefulness of pacing via the special lead may be limited by the failure of sensing and increased pacing threshold after shocks; Yee *et al* reported similar findings in 1984.[9] Internal cardioversion is not painless: patients receiving energy levels greater than 1 J required sedation and other groups have reported a similar pain threshold.[1 2 7] Further research is also needed to establish whether localised myocardial necrosis found at the site of delivery of high energy endocardial shocks has greater clinical importance than the more diffuse myocardial damage after repeated external countershock.[10]

Transvenous cardioversion offers advantages over external countershock but at present practical difficulties limit its application to patients with recurrent ventricular arrhythmias that cannot readily be controlled by conventional methods.

Medtronic Incorporated, Minneapolis, provided the cardioverter defibrillator and special leads.

References

1 Ciccone JH, Saksena S, Shah Y, Pantopoulos D. A prospective randomised study of the clinical efficacy and safety of transvenous cardioversion for termination of ventricular tachycardia. *Circulation* 1985;71:571–8.

2 Nathan AW, Bexton RS, Spurrell RAJ, Camm AJ. Internal transvenous low energy cardioversion for the treatment of cardiac arrhythmias. *Br Heart J* 1984;52:377–84.

3 Waspe LE, Kim SG, Matos JA, Fisher JD. Role of a catheter lead system for transvenous countershock and pacing during electrophysiological tests: an assessment of the usefulness of catheter shocks for terminating ventricular tachyarrhythmias. *Am J Cardiol* 1983;52:477–84.

4 Yee R, Zipes DP, Gulamhusein S, Kallok MJ, Klein GJ. Low energy countershock using an intravascular catheter in an acute cardiac care setting. *Am J Cardiol* 1982;50:1124–9.

5 Jackman WM, Zipes DP. Low energy synchronous cardioversion of ventricular tachycardia using a catheter electrode in a canine model of subacute myocardial infarction. *Circulation* 1982;66:187–95.

6 Saksena S, Chandran P, Shah Y, Boccadamo R, Pantopoulos D, Rothbart ST. Comparative efficacy of transvenous cardioversion and pacing in patients with sustained ventricular tachycardia: a prospective, randomised, crossover study. *Circulation* 1985;72:153–60.

7 Zipes DP, Jackman WM, Heger JJ, *et al.* Clinical transvenous cardioversion of recurrent life-threatening arrhythmias: low energy synchronised cardioversion of ventricular tachycardia and termination of ventricular fibrillation in patients using a catheter electrode. *Am Heart J* 1982;103:789–94.

8 Perelman MS, Rowland E, Krikler DM. Assessment of a prototype implantable cardioverter for ventricular tachycardia. Relation between synchronisation of sensing and origin of the tachycardia. *Br Heart J* 1984;52:385–91.

9 Yee R, Jones Klein GJ. Pacing threshold changes after transvenous cardioversion. *Am J Cardiol* 1984;53:503–7.

10 Dahl C, Ewy GA, Warner ED, Thomas ED. Myocardial necrosis from direct current counter-shock: effect of paddle electrode size and time interval between discharges. *Circulation* 1974;50:956–61.

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Detection of arrhythmias: use of a patient-activated ambulatory electrocardiogram device with a solid-state memory loop

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SUMMARY A patient-activated ambulatory electrocardiogram device with a solid-state memory loop was used to investigate 100 unselected patients experiencing palpitation, dizziness, or syncope. Clinically useful information was obtained in 68% of patients. Frequently, sinus rhythm had been restored by the time the patient activated the device, but the arrhythmia had been stored in the pre-event segment of the memory—a distinct advantage over many other patient-activated devices.

This recorder is complementary to conventional 24 hour electrocardiographic monitoring in the investigation of possible arrhythmias and is particularly suitable for patients with infrequent symptoms. Because the stored data can be rapidly analysed by any commercially available electrocardiograph the device is suitable for use in district general hospitals.

The role of ambulatory electrocardiographic monitoring is well established as a means of investigating cardiac rhythm disturbances.[1 2] Despite this, the assessment of patients who present with palpitation, dizziness, or syncope may be difficult. In some the cause of the symptoms is non-cardiac; in others in whom the symptoms are related to an arrhythmia the disturbance of rhythm may be short lived or infrequent and a single 24 hour ambulatory electrocardiogram may fail to detect the arrhythmia or fail to correlate an arrhythmia with the symptoms.[3]

Another approach to the problem has been the use of portable recorders that can be activated when the patient has symptoms.[4] These devices give no record of the rhythm preceding the acute event and arrhythmias lasting only a few seconds may not be detected at all.[5] As an alternative, we describe the use of a reliable and inexpensive patient-activated device that has a pre-event solid-state memory facility.

Patients and methods

The recorder, designed by one of us (JGD), weighs 320 g (with batteries) and measures 146 × 91 × 34 mm. It has no mechanical parts and uses a microprocessor to record a single channel electrocardiogram in a continuous 80 second loop. When the event button is pressed the loop stops and the data are stored in the solid state memory. The loop includes 70 seconds of rhythm before and 10 seconds after the button is pressed. When convenient (up to six months after recording) the stored data are printed as rhythm strips by connecting the recorder to any ordinary electrocardiograph.

We reviewed the results of 106 consecutive and unselected patients who had used the recorder over a three year period. The case notes from six patients were incomplete; we studied the remaining 100 patients (aged 16—88 years (median 58 years)). Twenty six patients complained of palpitation alone, 38 had experienced presyncope, and 36 syncope with or without palpitation. Symptoms occurred at least once per week in 53 patients, at least once per month in a further 35 patients, and less than once a month in the remaining 12 patients. Table 1 shows their previous histories.

Forty two patients had already had conventional 24 hour electrocardiographic tape monitoring and 17 (40%) had abnormal results. In these cases the solid state recorder was being used either because symptoms continued despite a change in treatment or because it was unclear whether the documented arrhythmias were the cause of the symptoms.

Each patient was fitted with the recorder for up to

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Table 1 *Previous medical history*

	No
No known cardiac disease	61
Ischaemic heart disease	23
Valvar heart disease:	
Mitral valve prolapse	5
Rheumatic mitral regurgitation	1
Aortic regurgitation	2
Aortic valve replacement	1
Atrial septal defect	2
Hypertrophic cardiomyopathy	2
Wolff-Parkinson-White syndrome	2
Dystrophia myotonica	1
(Total)	(100)

Table 2 *Rhythm detected*

	No
Paroxysmal tachycardia:	
Atrial fibrillation	10
Supraventricular tachycardia	3
Multiform ventricular tachycardia	1
Frequent extrasystoles (1 in 5 or more):	
Atrial	3
Ventricular	9
Occasional extrasystoles (atrial or ventricular)	27
Sinus tachycardia (> 120 beats/min)	10
Bradycardia:	
Junctional rhythm (rate 28 beats/min)	1
Sinus bradycardia (rate 25 beats/min)*	1
Sinus bradycardia and sinus arrest (> 13 s)	1
Sinus arrest (2 s)	1
Intermittent atrioventricular dissociation	2
No events	31
(Total)	(100)

*This patient had an episode of loss of consciousness and her husband pressed the event button. Because there was sinus bradycardia at the start of the recording the rhythm at the time of the acute event was never documented. She was paced and remains symptom free.

three weeks. The patient first returned to the electrocardiography department after recording two events or after one week. If no events had been recorded or if the rhythm was found to be sinus rhythm, or sinus rhythm with atrial or ventricular extrasystoles, new electrodes were applied and the patient was encouraged to continue recording for the remainder of the three week period.

Results

Of the 100 patients who used the recorder, 36 recorded one event and 33 made two or more recordings (table 2). For each patient only the most significant arrhythmia is shown. Fifty six patients made recordings that were considered completely diagnostic and these included 19 important arrhythmias. Thirteen further patients made recordings that were of some diagnostic value.

Fourteen episodes of paroxysmal tachycardia were recorded; multiform ventricular tachycardia was recorded in one patient (figure) and episodes of supraventricular tachycardia were recorded in the remainder. In five cases the arrhythmia was present at the start of the recording and the initiating event was not seen. Five of the patients with supraventricular tachycardia also had recordings showing sinus rhythm with infrequent atrial extrasystoles. In five of 14 cases of tachycardia and one of three cases of bradycardia the arrhythmia was only present in the pre-event segment of the memory (that is the patient had returned to sinus rhythm by the time the event button was pressed). All five patients with bradycardia or intermittent atrioventricular dissociation had suffered from syncope at some time; they therefore had a permanent endocardial pacemaker inserted and they remain symptom free.

Thirteen of the 19 patients with important arrhythmias had no previous cardiac history. Eight of the 12 patients with frequent extrasystoles had identical recordings on at least two occasions. The finding of normal sinus rhythm or occasional extrasystoles was regarded as diagnostic only if a similar recording was produced on two or more occasions in association with symptoms (14 of 27 patients). Thirty-one patients recorded no events; however, 10 of them had not used the recorder for the full three week period. Twelve of the patients with no events; had had infrequent symptoms (< 1 per month), and in seven drug treatment had been changed before they started to use the device.

Some patients found the recorder inconvenient to wear for long periods; other problems included loosening of the electrodes and patient interference with the recorder (for example removal of the batteries after recording had been made erased the memory). In the current model removal of the batteries does not erase the stored results which are backed up independently.

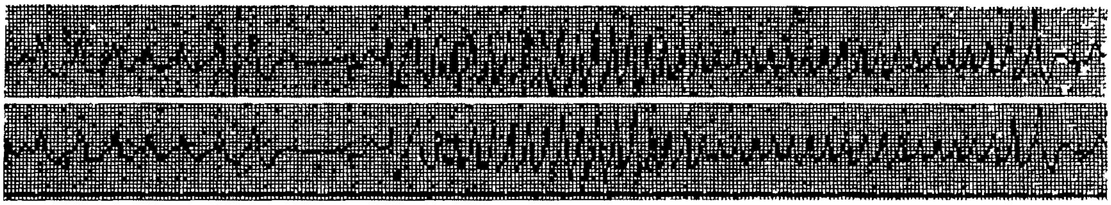

Figure *Solid state recording of an episode of multiform ventricular tachycardia.*

Table 3 *Comparison between 24 hour electrocardiographic tape and solid-state recorder*

	Solid-state recorder			
	Sinus rhythm or extrasystoles	*Definite abnormality*	*No events*	*Total**
24 ECG tape				
Sinus rhythm or extrasystoles	11	6	8	25
Definite abnormality	5	7	2	14

*We excluded three patients in whom drug treatment was changed between the two investigations.

Table 3 compares the results of recordings obtained with the solid-state device and a conventional 24 hour electrocardiogram.

Discussion

These results show that this solid-state recorder may be of considerable diagnostic value in the assessment of patients with palpitation, dizziness, or syncope. Among our patients, of whom two thirds gave no previous history of cardiac disease, important arrhythmias were demonstrated in 19% and a further 22% had multiple extrasystoles or sinus tachycardia. The "negative" finding of normal sinus rhythm or occasional extrasystoles in 27% is also of value because the patient could be reassured that no important rhythm disturbance coincided with the symptoms. These data compare favourably with conventional 24 hour electrocardiographic monitoring, which can be expected to provide useful diagnostic information in up to 65% of recordings.[6]

The pre-event segment of memory is useful in several ways. Firstly, the initiating sequence of a rhythm disturbance can be documented; this may be crucial to the accurate identification of an arrhythmia. Second, short lived arrhythmias may be documented; in this study six of 17 patients with paroxysmal arrhythmias had returned to sinus rhythm by the time the event button was pressed. In this subgroup a diagnosis would not have been made by conventional patient-activated devices which only record from the moment the button is pressed. This factor may account for the poor results obtained with the Cardiomemo recorder, a patient-activated device without a pre-event memory.[7]

In six patients 70 seconds of pre-event memory were insufficient to capture the onset of the arrhythmia. In our current model the timing sequence may be varied to enable one recording of 160 seconds to be made, two of 80 seconds, four of 40 seconds, or eight of 20 seconds. A single 160 second recording is particularly appropriate for the patient with syncopal attacks as it may take one or two minutes for the patient to recover consciousness and activate the event button.

We were surprised that we only documented a single episode of ventricular tachycardia because a preponderance of atrial arrhythmias was noted with other patient-activated devices.[4 8] This may merely reflect the relative frequency of supraventricular arrhythmias in a normal population[6]; an alternative explanation may be the small proportion (23%) of patients with ischaemic heart disease in this study.

Because the recorder will only provide a record of symptomatic arrhythmias it is not a substitute for traditional 24 hour electrocardiographic monitoring in circumstances where asymptomatic arrhythmias are likely (such as ischaemic heart disease and dilated or hypertrophic cardiomyopathy). The use of the recorder is therefore complementary to 24 hour tape monitoring rather than a substitute for it (table 3). Future modifications of the microprocessor program to facilitate automatic recordings at times of asymptomatic arrhythmias would be an advantage. Early experience with a commercially available instrument, the Instant Replay transtelephonic monitor (Instromedix Inc),[9] which includes many of the features of the device described in this paper, accords with our view of the usefulness of such recorders.

The simplicity of the recorder and the ease with which stored data can be analysed on standard equipment make the device suitable for use in district general hospitals.

References

1 McLeod AA, Jewitt DE. Role of 24-hour ambulatory electrocardiographic monitoring in a general hospital. *Br Med J* 1978;**i**:1197–9.

2 Winkle RA. Current status of ambulatory electrocardiography. *Am J Cardiol* 1981;**102**:757–70.

3 Petch MC. Lessons from ambulatory electrocardiography. *Br Med J* 1985;**291**:617–8.

4 Judson P, Holmes DR, Baker WP. Evaluation of outpatient arrhythmias utilizing transtelephonic monitoring. *Am Heart J* 1979;**97**:759–61.

5 Ward DE, Camm AJ. Ambulatory monitoring of transient arrhythmias. *Hospital Update* 1981;7:211–20.

6 Camm AJ, Ward DE, Spurrell RAJ. Arrhythmias in ambulatory persons: a review and experience of 1000 consecutive recordings. *Biotelemetry* 1978;5:167–81.

7 Thomas LE, Shapiro LM, Perrins EJ, Fox KM. Detection of arrhythmia: limited usefulness of patient activated recording devices. *Br Med J* 1984;**289**:1106–7.

8 Hasin Y, David D, Rogel S. Diagnostic and therapeutic assessment by telephone electrocardiographic monitoring of ambulatory patients. *Br Med J* 1976;**ii**:609–12.

9 Hardwin Mead R, Ruder MA, Winkle RA. The "Instant Replay" transtelephonic monitor: utility in the diagnosis of intermittent symptomatic arrhythmias. *PACE* 1986;**9**:311.

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Failure of propranolol to improve exercise tolerance in patients with mitral stenosis in sinus rhythm

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SUMMARY Propranolol reduces left atrial pressure at rest and during exercise in patients with mitral stenosis by lowering cardiac output and heart rate. Ten patients (aged 19–56) with moderate to severe isolated mitral stenosis were studied to determine whether propranolol increased their exercise tolerance. All were in sinus rhythm and free of left or right ventricular failure. Patients were trained in an individually graded bicycle or treadmill exercise protocol that provoked a reproducible degree of near maximal dyspnoea during the second three minute stage of exercise. Propranolol (80 mg or 120 mg) or matching placebo in two or three divided daily doses was given for one week in random double blind fashion. Exercise testing and questioning about subjective clinical response were carried out at the end of each week by an investigator who was unaware of the patient's heart rate. During propranolol treatment the heart rate was 19 beats/minute slower at rest and 38 beats/minute slower at peak exercise, but there was no change in mean exercise time to dyspnoea (274 s during propranolol *vs* 283 s during placebo). Four patients felt worse during the propranolol week, one patient felt better during the propranolol week, and five patients felt no difference between the two weeks.

Propranolol did not improve objective or subjective exercise tolerance in patients with isolated mitral stenosis in sinus rhythm.

The potential beneficial effect of β blockade in patients with mitral stenosis has been studied over the past 20 years.[1–3] The rationale for these investigations was the understanding that the pressure gradient across a stenotic mitral valve rises exponentially as the heart rate and cardiac output increase.[4] Thus the increases in heart rate and cardiac output that occur during exercise lead to higher left atrial and pulmonary venous pressure, which are the presumed cause of the exertional dyspnoea of mitral stenosis.[5] β blockade, by blunting the rises in heart rate and cardiac output during exercise, and thereby increasing the diastolic filling period and reducing transvalvar flow, would be expected to reduce the increase in pulmonary venous pressure at any given level of exercise. Indeed, in studies in which intravenous pronethalol[1] or propranolol[2 3] were given to patients with mitral stenosis during diagnostic cardiac catheterisation, heart rate and cardiac output were reduced, with an accompanying fall in left atrial pressure at rest and a reduced rise during exercise.[1–3] The usual conclusion of these studies was that long term treatment with β blockers would be likely to benefit patients with mitral stenosis.

Cumming and Carr, however, suggested that the negative inotropic effect of propranolol on the left ventricle, as well as the reduction in cardiac output, would be likely to cause an overall deterioration in cardiac performance, and thus the drug would not be of value in mitral stenosis.[6] Furthermore, β blockade has not gained widespread acceptance in the treatment of patients with mitral stenosis.[7] The only investigation of the effect of β blockade on exercise testing found that the treatment was of benefit; but the study was flawed by a single blind protocol and a poorly defined end point for cessation of exercise.[8]

To investigate further the potential benefit of the treatment of mitral stenosis with β blockade we have used an individually formulated exercise protocol to evaluate in a double blind trial the effect of propranolol on exercise tolerance in patients with mitral stenosis.

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Patients and methods

We studied ten patients with isolated mitral stenosis. The diagnosis was established by typical auscultatory, electrocardiographic, radiographic, and echocardiographic findings. The patients were in New York Heart Association functional class II or III and five had valve surgery 1–24 months after completing the study protocol. In eight patients the mitral valve area was estimated by cross sectional echocardiography while in the other two an estimation was available in the report of the operation (table). No patient had echocardiographic evidence of left ventricular enlargement or abnormal left ventricular function. None of the patients had evidence of right heart failure. No patient had obstructive lung disease or any other contraindication to β blockade.

Patients were trained according to an individual exercise protocol to reach a reproducible degree of near maximal dyspnoea. Five patients performed bicycle exercise and five exercised on a treadmill. Increments per three minute stage were 20 W and 1·0 kph respectively. In the training phase the patient became accustomed to the exercise laboratory and staff, recognised his dyspnoea end point, and attained a certain amount of physical conditioning. Achievement of stable performance (less than a 30 second variation in exercise duration) usually required 8–12 exercise bouts over several weeks with 2–3 bouts per session. There was invariably an improvement of at least one three minute stage during the training phase, and the starting level in watts or incline/speed for the study phase was chosen so that end point dyspnoea was reached after 3–6 minutes of exercise. At the final training session the patient was given a test dose of 40 mg of propranolol and was observed for several hours for possible adverse effects as well as for the degree of induced bradycardia.

During the study phase propranolol or matching placebo were given for one week each in randomised, double blind crossover fashion. The daily dose of propranolol was 80 or 120 mg (in two or three divided doses), according to body weight and the degree of bradycardia induced by the test dose. During a third week all patients except case 1 were given half the previous propranolol dose single blind. At the end of each week the patient was questioned in detail about beneficial or adverse effects by an investigator who did not know the patient's heart rate.

An exercise evaluation consisting of two bouts one hour apart was carried out at the end of each week. In order to maintain the double blind character of the study two investigators were present and one of them remained unaware of the patient's heart rate. Patients exercised according to the protocol that was established during the training phase. Patients were fasting. The dose of study medication was taken one and a half to two hours before the test. The patient's electrocardiogram was monitored continuously, and heart rate was recorded at rest, at three minutes, and at peak exercise. The investigator who remained unaware of the patient's heart rate stood out of view of the monitor, the recorder, and the clock, and decided with the patient when the end point of near maximal dyspnoea had been reached. This investigator then signalled the other investigator to stop the timer and record the heart rate. The blinded investigator then counted the number of respirations during the first minute after the end of exercise.

In patients 5–10 the blinded investigator measured the peak expiratory flow at the end of each week with a Wright peak flow minimeter.

We explained to each patient that this was a research study and obtained their informed consent. The study was approved by the institutional committee on research on human subjects.

STATISTICAL ANALYSIS

We used a mean of the two values for each exercise variable from the two bouts to represent the patient's exercise performance for that day. We used Student's t test for matched pairs to compare heart rates

Table *Data on individual patients*

Patient	*Age*	*Sex*	*Mitral valve area*	*Starting exercise level*
1	56	F	1·1 cm^2 E	40 W
2	41	F	"Severe stenosis" S	40 W
3	43	M	0·7 cm^2 E "Severe stenosis" S	60 W
4	39	F	1·0 cm^2 S	10 W
5	27	F	1·4 cm^2 E; 1·0 cm^2 S	40 W
6	35	M	1·7 cm^2 E	14%, 5·0 kph
7	40	F	1·3 cm^2 E	14%, 4·0 kph
8	49	M	0·9 cm^2 E	14%, 4·0 kph
9	19	F	1·2 cm^2 E, 1·1 cm^2 S	10%, 3·0 kph
10	38	M	0·8 cm^2 E	16%, 3·5 kph

E, Echocardiographic estimate, S, estimate at operation.

and exercise times during the placebo, propranolol, and half-dose propranolol weeks. Results are expressed as means (1 SE).

Results

Six patients received propranolol during the second week of the study. Mean heart rates were markedly lower during propranolol treatment than during placebo treatment: 55 (1) beats/min *vs* 74 (2) beats/min at rest ($p<0\cdot0001$); 103 (3) *vs* 132 (4) beats/min at 3 minutes exercise ($p<0\cdot0001$); and 115 (5) *vs* 151 (6) beats/min at peak exercise ($p<0\cdot0001$) (fig 1). All exercise bouts were stopped because of dyspnoea, and there was no difference in mean exercise time to near maximal dyspnoea between the propranolol and placebo weeks: 274 (25) s *vs* 283 (26) s (NS) (fig 2). During the third week, when patients received half the previous propranolol dose, heart rates were 63 (2) at rest, 115 (5) at three minutes, and 127 (4) at peak exercise ($p<0\cdot005$) for all values compared with placebo); but again there was no change in the mean duration of exercise (267 (23) s). The mean number of respirations during the first minute after exercise was 28 during propranolol treatment and 29 during placebo, indicating a similar degree of dyspnoea.

In response to questions about exertional dyspnoea, palpitation, fatigue, and overall wellbeing during the two blinded treatment weeks, five patients felt no difference between the two weeks, four patients felt worse on propranolol, and one patient felt slightly better on propranolol.

Among the six patients in whom peak flow rate was measured the mean rates were identical during placebo and propranolol treatment.

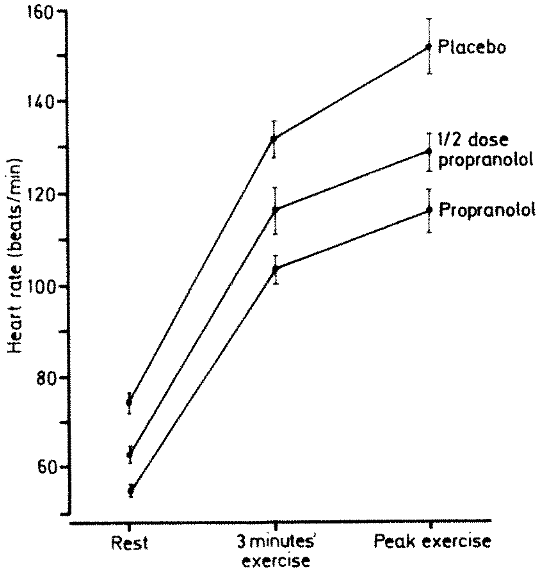

Fig 1 *Mean heart rates at rest after three minutes of exercise, and just before stopping exercise because of dyspnoea. Exercise tests were performed at the end of each treatment week.*

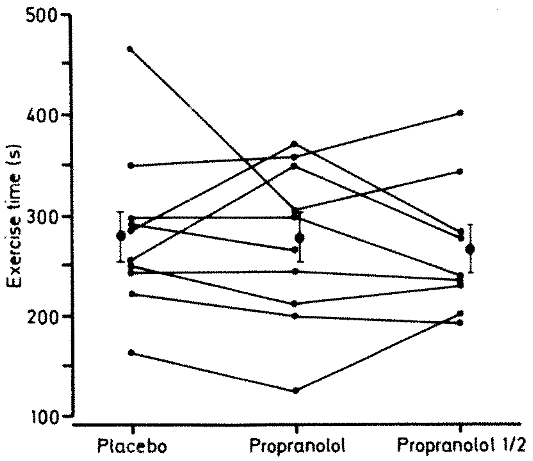

Fig 2 *Exercise times to near maximal dyspnoea during the exercise tests performed at the end of each treatment week. Individual results and group means (SE) are shown.*

Discussion

Despite haemodynamic observations that suggested that propranolol would be likely to increase exercise tolerance in patients with mitral stenosis,[1-3] our results indicate that treatment with this drug improves neither subjective nor objective exercise ability. The often poor correlation between improvement in haemodynamic variables in chronic heart failure and improvement in symptoms has been increasingly appreciated in recent years, and formal exercise testing is thus being used more frequently to evaluate changes in functional state in patients in heart failure.[9] In such cases it is crucial that the exercise test procedure objectively measures exercise capacity, and attention has been called to the subjectivity of symptomatic end points that are influenced by patient motivation and observer bias.[9] For this reason we trained our patients carefully before the experimental phase until a reproducible end point of near maximal dyspnoea was achieved; after this the study itself was carried out in double blind fashion.

In addition, in the minute immediately after exercise we measured the respiratory rate as a further indication of the degree of dyspnoea achieved. We used an individually formulated exercise protocol designed to produce a baseline exercise duration of 3–6 minutes on the model of the Redwood protocol[10] used in studying angina pectoris. Although exercise duration may be somewhat shorter than with standard exercise protocols, the briefer, more intense exercise is probably more similar to the type of effort that limits patients in their daily activities (for example two flights of stairs or 100 metres uphill). We have considerable experience with such a protocol in evaluating antianginal drugs, and have found that despite the shortness of the exercise, even extensively trained patients are capable of considerable increases in exercise duration after receiving an effective drug.[11] The end point of "near maximal dyspnoea" was defined to the patient as that degree of breathlessness which would cause him to rest during his ordinary exertion at a time when he was not in a particular hurry. Our subjects each performed a total of approximately 15 exercise bouts during the training and experimental phases of the study and we felt that it would be unfair to require them to exercise repeatedly to maximum dyspnoea or exhaustion. This might have made them less willing to complete the study.

In the only other investigation that used formal exercise testing to study the effect on exercise (it found β blockade to be of benefit) the patients were not trained, the end point was defined as "exhaustion, dizziness or severe dyspnoea", and the investigator supervising the exercise tests knew the patient's heart rate and thus could guess whether the patient was receiving a β blocker or a placebo.[8] Our own blinding procedure, however, prevented only the influence of a bias *in favour of* propranolol. Since the blinded investigator was aware of the patient's baseline exercise performance, a bias *against* the effectiveness of propranolol could have influenced the decision as to when to terminate an exercise bout. The effect of this potential influence was limited because the blinded investigator could not see the clock. In fact the original hypothesis was that propranolol would be effective; it was only when we were midway through the study that we adopted the opposite view.

Although we did not use large doses of propranolol we added a third week at half dose to be certain that we would not miss a therapeutic effect because of excessive β blockade. The reductions in heart rate at rest and at peak exercise were less than on the full doses of propranolol, but there was still no difference in exercise duration.

Although we did not measure pulmonary venous pressure, it is reasonable to assume, given the reductions in resting and exercise heart rates during treatment with β blocker, that the usual rise in pulmonary venous pressure seen during exercise in patients with mitral stenosis was blunted. Why then was there no concomitant improvement in exercise tolerance?

Although the classic view has been that the exertional dyspnoea of mitral stenosis is the result of the increased pulmonary venous pressure and volume that occurs during exercise,[12] the difficulty of separating the effects of pulmonary venous hypertension from the insufficient increase in cardiac output and oxygen delivery to exercising muscles has been long noted.[13] Failure to find a correlation between the degree of lung rigidity and the degree of dyspnoea suggested that the pulmonary changes in mitral stenosis might not be the primary cause of the dyspnoea.[13] Recent studies on the ventilatory responses to exercise in patients with chronic left ventricular failure have suggested that the exertional dyspnoea is primarily the result of the insufficient cardiac output and inadequate oxygen transport to working muscle, rather than of the increase in pulmonary venous pressure.[14 15] Although the patients in these studies had left ventricular failure rather than mitral stenosis,[14 15] the presence of the combination of a rise in pulmonary venous pressure in the face of an insufficient increase in cardiac output during exercise in both stages suggests that the same mechanism of dyspnoea may be operating. Thus while β blockade in patients with mitral stenosis might have a beneficial effect on pulmonary venous hypertension, the deleterious effect on the possibly more important factor of cardiac output may explain our failure to find a clinical improvement.

An additional explanation for the ineffectiveness of β blockade in mitral stenosis may be that right ventricular function is depressed. An abnormal right ventricular response to exercise has been demonstrated in patients with mitral stenosis in the absence of resting right ventricular failure,[16] and at the same time it has been shown that right ventricular ejection fraction is highly correlated with exercise capacity in patients with chronic left ventricular failure.[17]

Whatever the mechanism, the results of our study, which is the first double blind investigation of this issue, suggest that β blockade does not have a role in the treatment of patients with isolated mitral stenosis in sinus rhythm.

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References

1 Howitt G, Tinker J, Wade EG. The effect of pronethalol in mitral stenosis. *Clin Sci* 1965;**28**:417–26.
2 Meister SG, Engel TR, Feitosa GS, Helfant RH, Franke WS. Propranolol in mitral stenosis during sinus rhythm. *Am Heart J* 1977;**94**:685–8.

3 Giuffrida G, Bonzani G, Betocchi S, *et al*. Hemodynamic response to exercise after propranolol in patients with mitral stenosis. *Am J Cardiol* 1979;**44**:1076–82.

4 Gorlin R, Lewis BM, Haynes FW, Spigel RJ, Dexter L. Factors regulating pulmonary capillary pressure in mitral stenosis. IV. *Am Heart J* 1951;**41**:834–54.

5 Braunwald E. Valvular heart disease. In: Braunwald E, ed. *Heart disease. A textbook of cardiovascular medicine*. Philadelphia: WB Saunders, 1984:1066.

6 Cumming GR, Carr W. Hemodynamic response to exercise after beta adrenergic blockade with propranolol in patients with mitral valve obstruction. *Can Med Assoc J* 1966;**95**:527–31.

7 Braunwald E. Valvular heart disease. In: Braunwald E, ed. *Heart disease. A textbook of cardiovascular medicine*. Philadelphia: WB Saunders, 1984:1072.

8 Klein HO, Sareli P, Schamroth CL, Carim Y, Epstein M, Marcus B. Effects of atenolol on exercise capacity in patients with mitral stenosis with sinus rhythm. *Am J Cardiol* 1985;**56**:598–601.

9 Franciosa JA. Exercise testing in chronic congestive heart failure. *Am J Cardiol* 1984;**53**:1447–50.

10 Redwood DR, Rosing DR, Goldstein RE, Beiser GD, Epstein SE. Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris. *Circulation* 1971;**43**:618–28.

11 Bassan MM, Weiler-Ravell D, Shalev O. Comparison of the antianginal effectiveness of nifedipine, verapamil, and isosorbide dinitrate in patients receiving propranolol: a double-blind study. *Circulation* 1983;**68**:567–75.

12 Gazetopoulos N, Davies H, Oliver C, Deuchar D. Ventilation and haemodynamics in heart disease. *Br Heart J* 1966;**28**:1–15.

13 Hayward GW, Knott JMS. The effect of exercise on lung distensibility and respiratory work in mitral stenosis. *Br Heart J* 1955;**17**:303–11.

14 Franciosa JA, Leddy CL, Wilen M, Schwartz D. Relation between hemodynamic and ventilatory responses in determining exercise capacity in severe congestive heart failure. *Am J Cardiol* 1984; **53**:127–34.

15 Wilson JR, Ferraro N. Exercise intolerance in patients with chronic left heart failure: relation to oxygen transport and ventilatory abnormalities. *Am J Cardiol* 1983;**51**:1358–63.

16 Cohen M, Horowitz SF, Machac J, Mindich BP, Fuster V. Response of the right ventricle to exercise in isolated mitral stenosis. *Am J Cardiol* 1985;**55**:1054–8.

17 Baker BJ, Wilen MM, Boyd CM, Dinh H, Franciosa JA. Relation of right ventricular ejection fraction to exercise capacity in chronic left ventricular failure. *Am J Cardiol* 1984;**54**:596–9.

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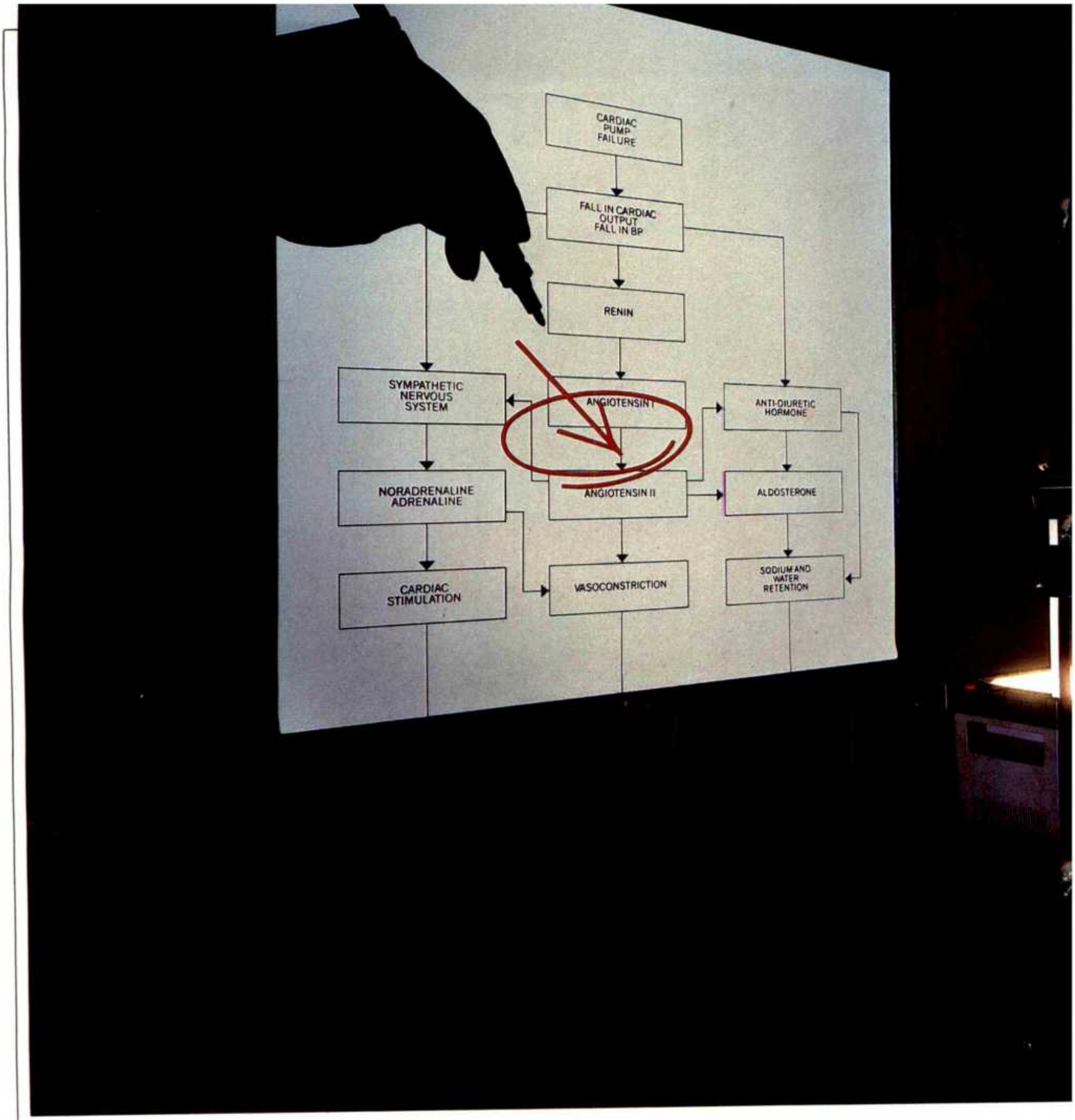

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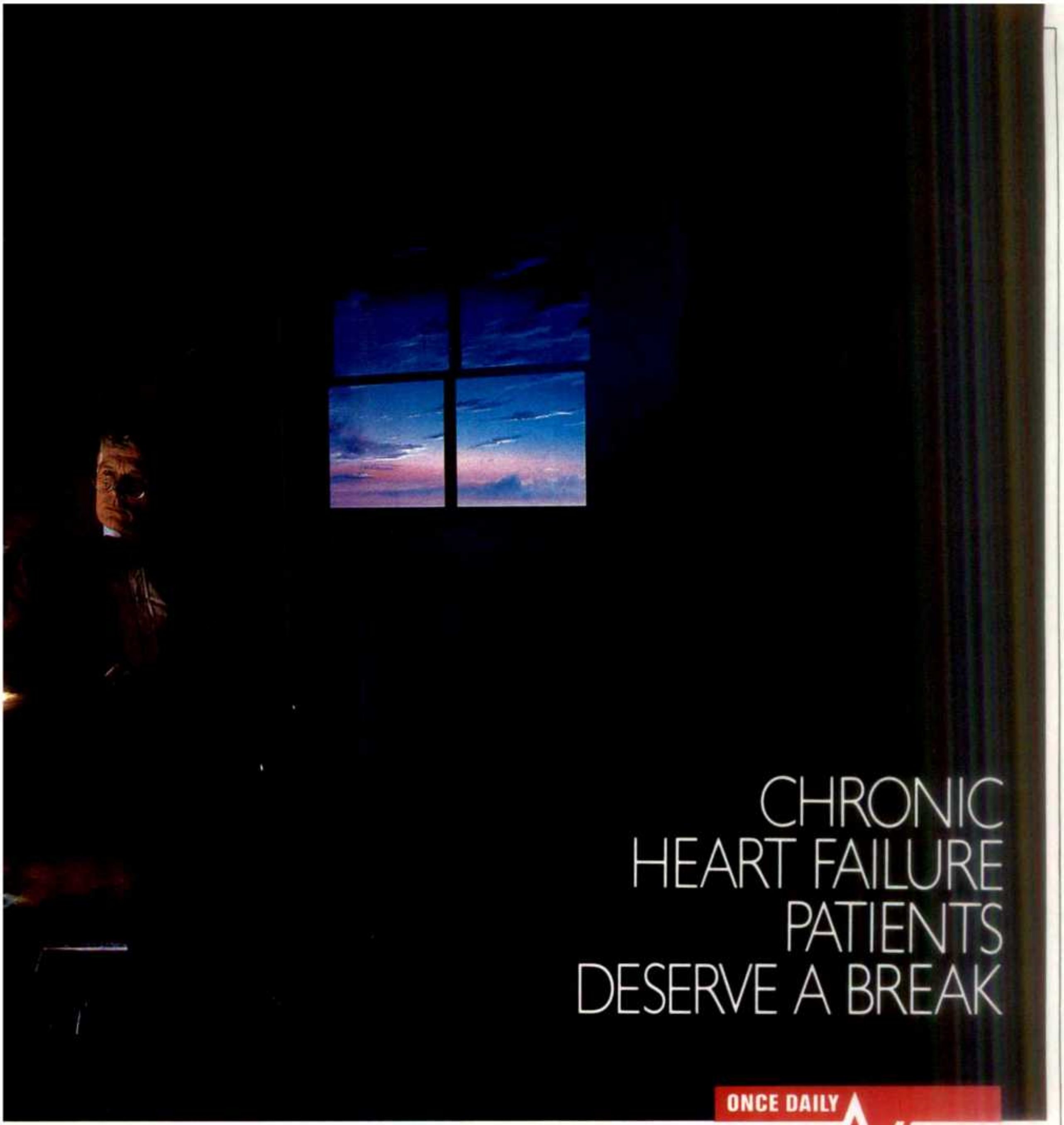

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'Innovace' may provide moderate to severe heart failure patients, even those clinically stable on diuretic therapy, with significant symptomatic improvement.

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Blood pressure and renal function should be monitored closely, both before and during treatment, because hypotension and renal impairment can occur. Reducing the dose of diuretics and starting therapy in hospital under close supervision with the recommended low dose of 2.5 mg of 'Innovace' helps minimise the incidence of early hypotension and facilitates initiation of therapy. Using 'Innovace' to break the *'vicious circle'* can go a long way to offer chronic heart failure patients benefits they may have not thought possible.

ABRIDGED PRODUCT INFORMATION

Full prescribing information is available and should be consulted before prescribing.

USES
All grades of essential hypertension and renovascular hypertension where standard therapy is ineffective or inappropriate because of adverse effects.

In congestive heart failure, as adjunctive therapy with digitalis and diuretics, treatment should always be initiated in hospital.

DOSAGE
Essential and renovascular hypertension: Therapy should be initiated with 5 mg in patients under 65 years of age; 2.5 mg if older or in presence of renal impairment. The usual maintenance dose is 10–20 mg once daily; maximum 40 mg once daily. When adding to a diuretic, the starting dose of 'Innovace' is 2.5 mg with the diuretic discontinued for 2–3 days prior to 'Innovace', if possible.

Reduce beta-blocker dose gradually after starting 'Innovace'. Dose titrate to BP requirements. Dosage of other antihypertensives may need adjusting.

Congestive heart failure: Can be used as adjunctive therapy with diuretics and, where appropriate, digitalis. Initial daily dose 2.5 mg under close supervision in hospital. If possible, diuretic dose should be reduced beforehand. Monitor blood pressure closely for hypotension.

Increase dose gradually to usual maintenance dose of 10–20 mg daily.

MODE OF ACTION
Following oral administration, 'Innovace' is rapidly absorbed and hydrolysed to enalaprilat, a highly specific, long-acting, non-sulphydryl angiotensin-converting enzyme inhibitor.

CONTRA-INDICATIONS
Pregnancy: assessment for possible pregnancy required if menstrual period is missed. Hypersensitivity.

PRECAUTIONS
Assess renal function prior to therapy with 'Innovace' and during treatment where appropriate. Should not be given with aortic stenosis or outflow tract obstruction.

Symptomatic hypotension is more likely following volume depletion caused by diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting or in patients with congestive heart failure with or without renal insufficiency. Severe hypotension reported mainly in patients with severe heart failure.

Impaired renal function: Caution should be used in patients with renal impairment. Renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Renal failure has been reported, mainly in patients with severe congestive heart failure or underlying renal disease, and is usually reversible. Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying artery stenosis. 'Innovace' is dialysable.

Renovascular hypertension: 'Innovace' can be used when surgery is not indicated or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases in blood urea and creatinine, reversible upon discontinuation of therapy, have been seen.

Because it is not known whether 'Innovace' is excreted in human milk, caution required if given to nursing mothers. Has not been studied in children.

Surgery/anaesthesia: 'Innovace' may lead to hypotension requiring volume expansion.

Drug interactions: Increased antihypertensive effect when combined with methyldopa, beta-blockers, calcium antagonists, or diuretics. Adrenergic-blocking drugs should be added with caution. Concomitant propranolol may reduce bioavailability. Lithium levels may be increased.

Plasma potassium usually remains within normal limits. 'Innovace' may elevate plasma potassium levels in patients with renal failure. Potassium supplements or potassium-sparing diuretics are not usually recommended, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. If deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

SIDE EFFECTS
Severe hypotension and renal failure.

Angioneurotic oedema has occurred rarely. Discontinue 'Innovace'; condition usually resolves without treatment, but give subcutaneous adrenaline (0.5 ml 1:1,000) if airways obstruction likely.

Most frequently, dizziness, and headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, urticaria, dysgeusia, and cough.

Clinical laboratory findings: Increased blood urea and plasma creatinine, decreases in haemoglobin, platelets, white cell count, and elevation of liver enzymes have occurred in a few patients, but causal relationship not established.

Overdosage: Hypotension most likely manifestation.

BASIC NHS COST
Tablets 20 mg: calendar packs of 28 tablets, £13.10; bottles of 50 tablets, £23.40. Tablets 10 mg: calendar packs of 28 tablets, £11.03; bottles of 50 tablets, £19.69. Tablets 5 mg: calendar packs of 28 tablets, £7.86; bottles of 50 tablets, £14.03. Tablets 2.5 mg: Bottles of 50 tablets, £10.

PRODUCT LICENCE NUMBERS
Tablets, 2.5 mg, 0025/0220; Tablets, 5 mg, 0025/0194; Tablets, 10 mg, 0025/0195; Tablets, 20 mg, 0025/0196.

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Inheritance of hypertrophic cardiomyopathy: a cross sectional and M mode echocardiographic study of 50 families

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A M O VEALE‡

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SUMMARY To determine the mode of inheritance of hypertrophic cardiomyopathy 193 first degree relatives (parents, siblings, and offspring) of 50 patients with hypertrophic cardiomyopathy were assessed by clinical examination, electrocardiography, M mode and cross sectional echocardiography, and necropsy when available. Thirty nine (20%) first degree relatives had hypertrophic cardiomyopathy—37% of parents, 25% of siblings, and 8% of offspring. Eight (23%) of 35 affected relatives diagnosed by echocardiography had normal clinical and electrocardiographic findings. In the total study group 43% of the male population and 30% of the female population were affected. This difference is statistically significant. In 28/50 families there was familial occurrence of hypertrophic cardiomyopathy. Familial occurrence was demonstrated in 17 of 18 families in which five or more family members were assessed. In 15 families the pattern of inheritance was consistent with an autosomal dominant trait; in the other 13 the affected members were identified in a single generation and the pattern of inheritance could not be determined.

The familial occurrence of hypertrophic cardiomyopathy is well documented. Before the development of echocardiography one third of cases were considered "genetic" and two thirds "sporadic".[1 2] With the widespread use of echocardiography in the 1970s, many cases of hypertrophic cardiomyopathy were diagnosed in patients without clinical evidence of the disease.[3] M Mode echocardiography studies suggested that about 50% of first degree relatives of cases were affected and that hypertrophic cardiomyopathy was probably always transmitted as an autosomal dominant trait with a high degree of penetrance.[4–6]

The accuracy of echocardiographic diagnosis of hypertrophic cardiomyopathy has increased with the introduction of cross sectional echocardiography, better understanding of the criteria for the diagnosis,[7] and an appreciation of the morphological spectrum of the disease.[8 9] In a recent cross sectional and M mode echocardiographic study of 70 families with hypertrophic cardiomyopathy 56% showed familial occurrence of the disease.[10] Twenty two per cent of first degree relatives were affected. Parents and siblings were affected more frequently than offspring. The most common pattern of inheritance was autosomal dominant but 44% of cases were apparently sporadic.

We have investigated the inheritance of this disease in a New Zealand population.

Patients and methods

SELECTION OF PATIENTS

The study protocol was approved by the Green Lane Hospital ethics committee. Seventy patients met our selection criteria as probands: (*a*) review at Green Lane Hospital between January 1964 and May 1984, (*b*) characteristic clinical features of hypertrophic cardiomyopathy supported by echocardiographic or haemodynamic and angio-

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cardiographic studies or both, (*c*) residence within 200 km of Green Lane Hospital at time of presentation, (*d*) presentation independent of a family history of hypertrophic cardiomyopathy. Dead patients were included as probands. In two instances in which two first degree relatives met these criteria the subject presenting first was considered to be the proband. Four probands were related (an uncle and nephew in one family, two first cousins in a second family). Twenty patients were excluded: 12 were lost to follow up, six had no first degree relatives available for study, and two were unwilling to participate in the study.

During 1984, 39 probands were reassessed at Green Lane Hospital. Nine probands had died, and two were not available for reassessment. The 50 probands had a total of 341 first degree relatives. One hundred and seventy eight first degree relatives assessed at Green Lane Hospital had cross sectional and M mode echocardiographic studies adequate to confirm or exclude hypertrophic cardiomyopathy. Two first degree relatives had been previously assessed at Green Lane Hospital. Diagnostic information was obtained on eight first degree relatives assessed in other centres,* and necropsy information adequate to confirm (four relatives) or exclude (one relative) hypertrophic cardiomyopathy was obtained on five first degree relatives.

We attempted to establish the cause of death in all dead first degree relatives from death certification, medical, hospital, and necropsy reports. We were unable to confirm or exclude hypertrophic cardiomyopathy in 148 first degree relatives (82 were dead and inadequate clinical/necropsy data were available, 47 lived in areas too remote from Green Lane Hospital, 10 were unwilling to participate in the study, and in nine echocardiographic studies were technically inadequate or systemic hypertension precluded definitive classification).

The final study group consisted of 50 probands (28 male, 22 female) and 193 first degree relatives (100 male, 93 female) (table 1). Twenty two probands and two first degree relatives had undergone septal myotomy-myectomy at Green Lane Hospital. All subjects assessed at Green Lane Hospital underwent clinical examination, 13 lead electrocardiography, and M mode and cross sectional echocardiography.

A detailed family history of proband patients was taken including all first degree and second degree (grandchildren, nieces and nephews, aunts and uncles, grandparents) relatives. There was no evidence of consanguinity in any family.

SYMPTOMS AND CLINICAL EXAMINATION

The symptomatic state was recorded preoperatively for probands (22) and relatives (2) undergoing septal myotomy-myectomy and at time of assessment for subjects (65) not treated surgically. The symptomatic state was not recorded in one affected first degree relative because of severe coexisting obstructive lung disease and in two relatives the symptomatic state was unknown. Resting supine blood pressure was measured on two occasions at least 60 minutes apart and the lower of the two measurements was recorded. Subjects were classified as hypertensive if (*a*) there was a history of hypertension or (*b*) blood pressures were consistently >140/90 mm Hg. Audible fourth heart sounds (or a palpable presystolic impulse), systolic murmurs of grade II/VI intensity or greater, and diastolic murmurs were recorded as abnormal. Third heart sounds in patients less than 20 years and systolic murmurs of grade I/VI intensity were not recorded as abnormal.

ELECTROCARDIOGRAPHY

Electrocardiogram data were available for review in all probands and in 184 of 193 first degree relatives. Left ventricular hypertrophy, atrial hypertrophy, abnormal Q waves (>0·04 s and >25% of the R wave), rhythm and conduction abnormalities were documented on a resting 13 lead electrocardiogram.

Table 1 *Demographic data in probands, affected relatives, and unaffected relatives, excluding relatives with "probable" hypertrophic cardiomyopathy*

Subject Characteristics	*Probands*	*Parents*		*Siblings*		*Offspring*	
		Affected	*Unaffected*	*Affected*	*Unaffected*	*Affected*	*Unaffected*
No with definite hypertrophic cardiomyopathy	50	11	16	22	64	6	66
Mean age (years)	54·7	62·0	61·1	39·4	37·3	26·5	23·2
(SD)	(10·1)	(16·1)	(14·9)	(17·9)	(16·5)	(21·0)	(12·8)
Median age (years)	60	67	65	36	39	24·5	22·5
Age range (years)	43–61	32–81	34–81	7–75	8–72	8/12*–63	3–60

*Eight months.

---

*Information supplied by Dr A P Poole, Southland Hospital, Invercargill; and Dr R N Easthope, Wellington Hospital.

The minimum criterion for left ventricular hypertrophy was a voltage ($SV_1 + RV_6^2$ or $SV_2 + RV_6$) of 35–60 mm (45–60 mm in children less than 18 years).[11] Electrocardiogram data were recorded preoperatively in subjects undergoing septal myotomy-myectomy.

ECHOCARDIOGRAPHY

Cross sectional echocardiographic studies were performed with a Toshiba SSH 10A electronic phased array sector scanner with a 2·4 MHz transducer. Images were recorded on ¾ inch video cassette for subsequent review. M mode echoes were obtained simultaneously with direct visualisation by means of the cross sectional scanner and were recorded with a Honeywell model L56AHS stripchart recorder interfaced with the sector scanner.

The thickness of the interventricular septum and posterior free wall was measured at the onset of the QRS complex in the same cardiac cycle with the ultrasound beam directed slightly caudal to the mitral valve leaflets. The leading edge method was used.[12] M mode measurements were compared with normal values related to age and body weight measured during the same phase of the cardiac cycle.[13]

Cross sectional echocardiograms of parasternal long and short axis, apical four and two chamber, and subcostal views were recorded.[12] Short axis left ventricular views were obtained by orienting the transducer perpendicularly to the long axis of the left ventricle from a parasternal location where the septum was most nearly perpendicular to the ultrasound beam. Serial short axis views were obtained during a sweep performed by maintaining the transducer in a fixed location on the chest wall and angling the image plane from aorta to apex. Emphasis was placed on achieving images in which the entire left ventricular endocardium and epicardium were well defined and in which the left ventricular cavity was most nearly circular.

Assessment of hypertrophy on cross sectional recordings was assessed by careful review of the real time recording and by measurement of wall thickness directly from the video screen with callipers. All M mode and cross sectional echocardiographic recordings were assessed by two independent observers (SCG, AHGR). Where there was disagreement (three patients) the echocardiograms were jointly reviewed and a decision reached.

DIAGNOSTIC CRITERIA FOR HYPERTROPHIC CARDIOMYOPATHY

The diagnostic criterion for hypertrophic cardiomyopathy was left ventricular hypertrophy without dilatation of the left ventricular cavity in the absence of another cardiac or systemic disease capable of causing left ventricular hypertrophy. On M mode echocardiography, the criteria for left ventricular hypertrophy was increased wall thickness (interventricular septum (IVS) only or interventricular septum and posterior free wall (PFW)) clearly greater than the upper 95% confidence interval.[13] Asymmetrical septal hypertrophy (IVS:PFW $\geqslant 1{\cdot}3$) without clear evidence of left ventricular hypertrophy was not a criterion (16 subjects). On cross sectional echocardiography hypertrophy was considered to be present if wall thickness was clearly $\geqslant 15$ mm in subjects who were $\geqslant 16$ years. In subjects < 16 years hypertrophy was considered to be present if wall thickness was $\leqslant 3$ mm than the upper 95% confidence interval of M mode recordings.[13]

Five probands and six first degree relatives designated as having hypertrophic cardiomyopathy had a history of systemic hypertension but were included because of clinical features suggestive of hypertrophic cardiomyopathy or because the degree of left ventricular hypertrophy on echocardiography clearly exceeded that attributable to the hypertension.

Eight relatives were designated as having probable but not definite hypertrophic cardiomyopathy because (*a*) systemic hypertension obscured the diagnosis (three subjects); (*b*) ventricular wall thicknesses were borderline (four subjects); (*c*) in one dead subject available clinical data strongly suggested hypertrophic cardiomyopathy but no diagnostic echocardiographic or necropsy information was available.

STATISTICAL ANALYSIS

Modes of inheritance in the study group were analysed by a simple segregation analysis which determined the proportion of first degree relatives affected by hypertrophic cardiomyopathy. Affected first degree relatives were counted after excluding the proband from the pedigree.

The 95% confidence intervals for segregation ratios (proportion of first degree relatives affected) are the 95% confidence intervals for the binomial distribution. They were achieved by logistic transformation, which gives asymmetric confidence limits. This gives a more precise definition of group limits than methods giving symmetrical limits.[14]

Student's unpaired *t* test and χ^2 test were used where appropriate.

Results

DIAGNOSIS IN RELATIVES

Definite hypertrophic cardiomyopathy was diagnosed in 35 first degree relatives by echocardiography and in four by review of necropsy and clinical records. Of the 35 diagnosed by echocardiography, eight (23%) had normal clinical examinations and electrocardiogram, one (3%) had an abnormal clinical examination but normal electrocardiograms, 10 (29%) had an abnormal electrocardiogram but normal clinical examination, and 16 (46%) had abnormal features on both clinical examination and electrocardiograms (fig 1). Of these 35 relatives diagnosed by echocardiography, 11 (31%) had previously been diagnosed as having hypertrophic cardiomyopathy, six (17%) had been previously known to have a cardiac abnormality not diagnosed as hypertrophic cardiomyopathy, and 18 (51%) were not known to have any cardiac abnormality before the study.

SEGREGATION RATIO

Thirty nine (20%) of 193 first degree relatives were affected with hypertrophic cardiomyopathy (fig 2). If those patients classified as having probable hypertrophic cardiomyopathy are included, 47/193 (24%) were affected. The frequency of definite cases in offspring (6/74, 8%) was significantly less than that in siblings (22/89, 25%, $p < 0·005$) or parents (11/30, 37%, $p < 0·005$) (fig 2). The difference between parents and siblings was not statistically significant. If those patients with probable hypertrophic cardiomyopathy are included, 47% of parents, 28% of siblings, and 11% of offspring were affected (difference between parents and siblings, NS; parents and offspring, $p < 0·001$; siblings and offspring, $p < 0·005$). Among parents, siblings, and offspring males were affected more frequently than females (fig 2). In the total group of probands and first degree relatives, 55 (43%) of 128 of the male population and 34 (30%) of 115 of the female population were affected ($p < 0·05$).

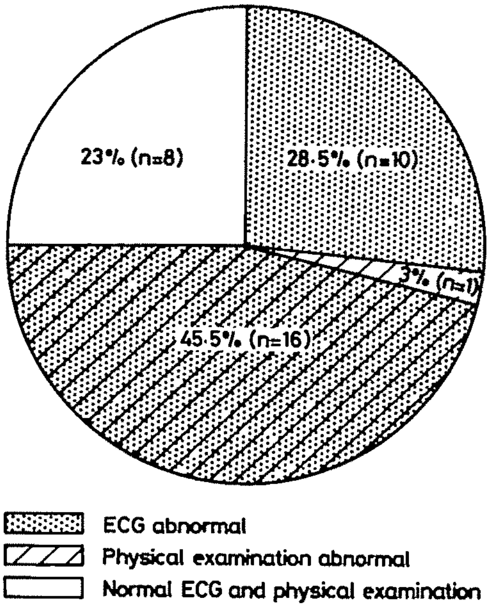

Fig 1 *Numbers and percentages of 35 first degree relatives diagnosed by echocardiography as having hypertrophic cardiomyopathy who also had clinical and electrocardiographic abnormalities.*

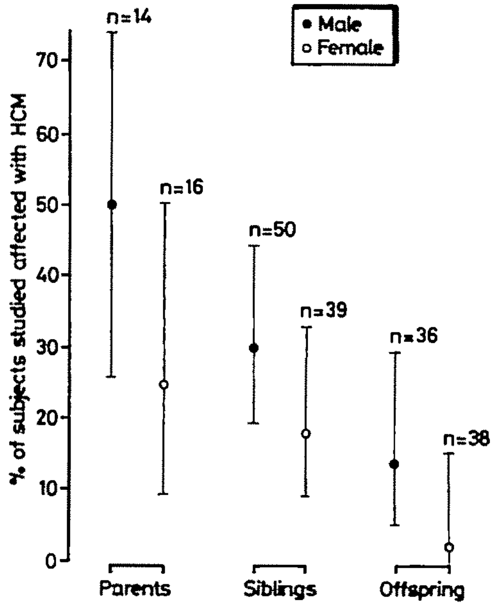

Fig 2 *Numbers and percentages of parents, siblings, and offspring studied with definite hypertrophic cardiomyopathy. Ninety five per cent confidence intervals are shown and each group is separated into male and female subjects.*

Twenty eight of 50 pedigrees showed familial occurrence of definite hypertrophic cardiomyopathy. The frequency with which hypertrophic cardiomyopathy was identified in relatives increased with the number of subjects studied (table 2). In these 28 pedigrees, 67% of all first degree relatives were studied. In the 22 pedigrees in which no relatives were affected, 40% of all first degree relatives were studied ($p < 0·01$).

All pedigrees were examined for features of autosomal dominant, recessive, and X-linked inheritance. In 15 pedigrees with hypertrophic cardiomyopathy in successive generations there were 16 instances of transmission from one generation to the next. Male to male transmission occurred in eight cases, male to female transmission in three cases, female to female transmission in one case, and female to male transmission in four cases. Male to male transmission excludes X-linked recessive

Table 2 *Frequency of familial hypertrophic cardiomyopathy (HCM) related to the number of first degree relatives studied*

Number of first degree relatives studied	*Number of pedigrees*	*Number and percentage of pedigrees with familial HCM*
1	11	3 (27%)
2	8	5 (63%)
3	4	1 (25%)
4	9	2 (22%)
5	5	4 (80%)
6	5	5 (100%)
7	4	4 (100%)
8	3	3 (100%)
9		
10		
11	1	1 (100%)
Total	193	28

inheritance and X-linked dominant inheritance.

In 15/28 pedigrees the pattern of inheritance was most consistent with an autosomal dominant trait—that is affected relatives were identified in successive generations. In the other 13 pedigrees affected relatives were identified in only one generation and the pattern of inheritance could not be specified. Detection of hypertrophic cardiomyopathy in parents and siblings (but not offspring) of probands was related to the percentage studied (table 3).

For seven probands both parents were available for study. One parent was affected in five pairs and both parents were normal in two pairs. All siblings in the latter two families were studied. In the first, one of five siblings was affected and in the second all three siblings were normal. Neither of the two probands had children. These two pedigrees may represent recessive inheritance, incomplete penetrance or, in the second case, sporadic disease.

The low frequency of hypertrophic cardiomyopathy in offspring raises the possibility that hypertrophic cardiomyopathy is a progressive disorder which may develop later in life. Regression equations were derived to determine the change in interventricular septal thickness with age in normal subjects, probands, and affected relatives.

$y = b x + a (\pm sy{:}x)$ where y = septal thickness (as percentage of predicted); x = age; b = slope; a = intercept; s = a constant.

When corrected for weight and for the normal slight increase that occurs with age,[12] interventricular septal thickness did not change appreciably with age in normal subjects (fig 3) ($p = 0{\cdot}31$) and tended to be greater with increasing age in affected relatives (fig 4) but this was not statistically significant ($p = 0{\cdot}26$). An apparent inverse trend with age in probands (fig 5) (just significant $p = 0{\cdot}048$) is probably related to exclusion of severely affected subjects from older age groups by death or operation. The mean and median ages were similar in affected and non-affected parents, siblings, and offspring (table 1). Thus although septal thickness may increase with age we have no clear evidence that hypertrophic cardiomyopathy is a progressive disorder; however, individual serial studies have not been undertaken.

Discussion

There are several methodological problems and sources of bias that make the study of genetic disease difficult and are relevant to this study. (*a*) Many individuals with hypertrophic cardiomyopathy are symptom free and would not normally come to clinical attention. Thus the selection of proband patients is biased. Families with more than one affected member are more likely to be ascertained, producing bias against the detection of sporadic cases. (*b*) The definitive diagnosis of hypertrophic cardiomyopathy usually requires echocardiographic or detailed necropsy study. Because this was a retrospective study such information was not available in 148 first degree relatives and in these individuals hypertrophic cardiomyopathy could not be excluded or confirmed. In addition, a small number of first degree relatives studied could not be classified definitively because of coexisting systemic hypertension.

Previous M mode echocardiographic studies have

Table 3 *Numbers and percentages of relatives studied in pedigrees in which hypertrophic cardiomyopathy (HCM) was identified in successive generations or in a single generation, and in pedigrees with no relatives affected*

	Number and percentage of parents studied	*Number and percentage of siblings studied*	*Number and percentage of offspring studied*	*Number and percentage of all first degree relatives studied*
HCM identified in successive generations (15 pedigrees)	16 (53%)	32 (71%)	24 (89%)	72 (71%)
HCM identified in a single generation (13 pedigrees)	7 (27%)	38 (66%)	20 (95%)	65 (62%)
HCM not identified in first degree relatives (22 pedigrees)	7 (16%)	19 (31%)	30 (83%)	56 (40%)
All pedigrees	30 (30%)	89 (54%)	74 (88%)	193

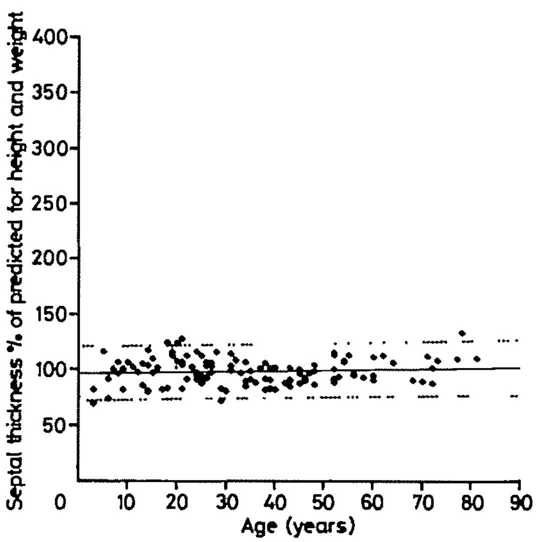

Fig 3 *Relation of interventricular septal (IVS) thickness to age in normal subjects (septal thickness expressed as percentage of predicted related to age and body weight). Regression equation: IVS thickness (percentage of predicted) = 0·059590 × age + 97·2723 (±12·1325).*

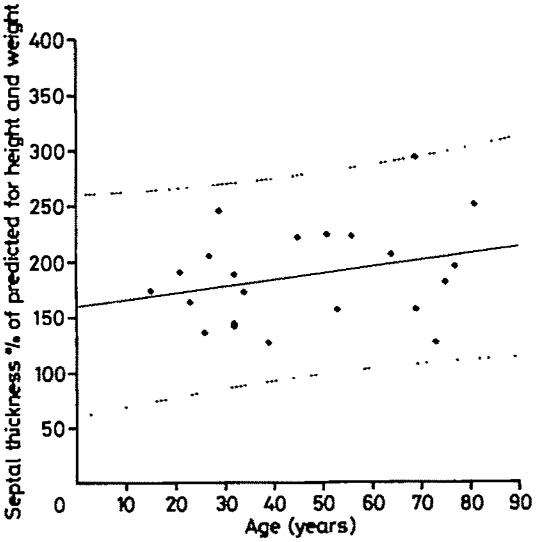

Fig 4 *Relation of interventricular septal (IVS) thickness to age in 22 affected relatives of subjects with hypertrophic cardiomyopathy (septal thickness expressed as percentage of predicted related to age and body weight). Regression equation: IVS thickness (percentage of predicted) = 0·499094 × age + 161 364 (±43 0955).*

suggested that hypertrophic cardiomyopathy is usually transmitted as an autosomal dominant trait with high penetrance.[4–6] Our data confirm the finding of Maron *et al*[10] that approximately 20% of first degree relatives of subjects with hypertrophic cardiomyopathy are shown to be affected when they are studied by M mode and cross sectional echocardiography.

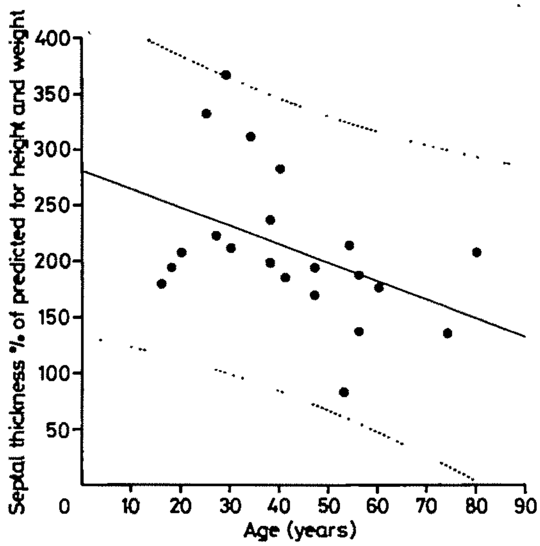

Fig 5 *Relation of interventricular septal (IVS) thickness to age in 21 probands with hypertrophic cardiomyopathy (septal thickness expressed as percentage of predicted related to age and body weight). Regression equation: IVS thickness (percentage of predicted) = −1 65384 × age + 281·445 (±61·5441).*

Factors which may have contributed to the lower yield with cross sectional echocardiography are: (*a*) differences in population structure (in our study and in that of Maron *et al*[10] offspring and siblings were affected significantly less frequently than parents and siblings, and comparatively large numbers of offspring were included in these studies (table 4)); (*b*) cross sectional echocardiography is more accurate than M mode echocardiography in defining the right and left sides of the interventricular septum and in avoiding oblique angulation of the ultrasound beam; (*c*) asymmetrical septal hypertrophy (ratio of septal to posterior wall thickness ≥1·3) used by Clark *et al* and Van Dorp *et al*,[4 5] without clear evidence of left ventricular hypertrophy, is not a reliable diagnostic criterion for hypertrophic cardiomyopathy. Neither is an absolute septal thickness of ≥1·3 cm unrelated to age and body weight (Bjarnason *et al*[6]). It is unclear from Clark *et al* and Van Dorp *et al*[4 5] how many individuals were diagnosed solely on the basis of a ratio. Sixteen subjects in our study had asymmetrical septal hypertrophy but were not regarded as having definite hypertrophic cardiomyopathy. Because of inaccurate diagnostic criteria and technical limitations, M mode echocardiography has probably overestimated the percentage of first degree relatives affected in families

Table 4 *Numbers of parents, siblings, and offspring studied in genetic studies of hypertrophic cardiomyopathy*

	Total relatives studied	*No of parents and siblings studied as % of total*	*Percentage of parents and siblings affected*	*No of offspring studied as % of total*	*Percentage of offspring affected*
Clark *et al*[4]	105	72 (69%)	53%	33 (31%)	30%
Bjarnason *et al*[6]	44	35 (80%)	46%	9 (20%)	20%
Maron *et al*[10]	296	157 (53%)	28%	139 (47%)	14%
Greaves *et al*	193	119 (62%)	28%	74 (38%)	8%

Van Dorp *et al*[5] excluded from analysis because of inclusion of first cousins.

with hypertrophic cardiomyopathy.

Fifty six per cent of all pedigrees showed familial occurrence of hypertrophic cardiomyopathy. The frequency with which hypertrophic cardiomyopathy was identified in first degree relatives increased with the number of subjects studied. Hypertrophic cardiomyopathy was identified in 67% of 30 families where three or more first degree relatives were studied, and in 95% of 18 families where five or more relatives were studied, indicating a strongly familial trait.

On inspection of individual pedigrees, autosomal dominant transmission was documented in 15 of 28. The 13 pedigrees in which hypertrophic cardiomyopathy was detected in only one generation may reflect different modes of inheritance, reduced penetrance (that is genetic disease not overtly expressed as hypertrophic cardiomyopathy) or failure to identify the disease because of the previously mentioned limitations of a retrospective analysis. In these 13 pedigrees fewer parents were studied, and fewer probands had three generations available for study; in two of these 13 pedigrees, and in 16 of the 22 pedigrees in which hypertrophic cardiomyopathy was not identified in first degree relatives, only one generation was studied, so that autosomal dominant inheritance could not be proved. The 22 apparently isolated cases of hypertrophic cardiomyopathy may in some cases reflect recessive inheritance, new genetic mutation, or non-genetic disease. However, because we included 12 probands with only one or two relatives available for study, it is probable that some have familial disease that could not be confirmed in this study.

The frequency with which hypertrophic cardiomyopathy was found in subgroups of first degree relatives is similar to that noted by Maron *et al.*[10] Parents were affected most often and offspring least often. In all subgroups more males were affected than females. In the total group of probands and first degree relatives males were affected significantly more frequently than females ($p < 0.05$). Maron *et al* also found a significant difference in the percentages of males (26%) and females (17%) affected in the total study group ($p < 0.001$).[10]

One quarter of affected first degree relatives had normal clinical and electrocardiographic findings and were diagnosed only by echocardiography. The course in this group of patients is uncertain. One of them was the parent of a proband with severe diffuse left ventricular hypertrophy, suggesting that the genetic implications of such an isolated echocardiographic finding may be similar to that of more overt hypertrophic cardiomyopathy.

The major question that arises in genetic counselling is the risk of transmission of the disease to offspring. Only 8% of offspring were affected in this study. It is possible that hypertrophic cardiomyopathy is a progressive disease that is not always apparent at a young age. Maron *et al* have documented the spontaneous appearance and progression of left ventricular hypertrophy in adolescent relatives of patients with hypertrophic cardiomyopathy.[15] Bjarnason *et al* found a positive correlation of septal thickness with age.[6] We were unable to show significant progression of septal hypertrophy in affected individuals and the mean and median ages of affected and unaffected parents, siblings, and offspring were similar. The median age of unaffected offspring was 22·5 years. We therefore do not have evidence that hypertrophic cardiomyopathy is a progressive disease. Further serial studies of individual patients will be necessary to confirm Maron's finding.

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References

1 Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis: I. A description of the disease based upon an analysis of 64 patients. *Circulation* 1964;30(suppl IV):IV-3–119.

2 Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history. *Circulation* 1968;37:759–88.

3 Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy (ASH): echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation* 1973;47:225–33.

4 Clark CE, Henry WL, Epstein SE. Familial prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis. *N Engl J Med* 1973;289:704–14.

5 Van Dorp WG, ten Cate FJ, Vletter WB, Dohman H, Roelandt J. Familial prevalence of asymmetric septal hypertrophy. *Eur J Cardiol* 1976;4:349–51.

6 Bjarnason I, Jonsson S, Hardarson T. Mode of inheritance of hypertrophic cardiomyopathy in Iceland. Echocardiographic study. *Br Heart J* 1982;47:122–9.

7 Maron BJ, Epstein SE. Hypertrophic cardiomyopathy. Recent observations regarding the specificity of three hallmarks of the disease: asymmetric septal hypertrophy, septal disorganisation and systolic anterior motion of the anterior mitral leaflet. *Am J Cardiol* 1980;45:141–54.

8 Maron BJ, Gottdiener JS, Bonow RD, Epstein SE. Hypertrophic cardiomyopathy with unusual locations of left ventricular hypertrophy undetectable by M-mode echocardiography: identification by wide-angle, two-dimensional echocardiography. *Circulation* 1981;63:409–18.

9 Yamaguchi H, Ishimura T, Nishiyamas S, *et al.* Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy). Ventriculographic and echocardiographic features in 30 patients. *Am J Cardiol* 1979;44:401–12.

10 Maron BJ, Nichols PF, Pickle LW, Wesley YE, Mulvihill JJ. Patterns of inheritance in hypertrophic cardiomyopathy: assessment by M-mode and two-dimensional echocardiography. *Am J Cardiol* 1984;53:1087–94.

11 Smith HJ, Neutze JM, Roche AHG, Agnew TM, Barratt-Boyes BG. The natural history of rheumatic aortic regurgitation and the indications for surgery. *Br Heart J* 1976;38:147–54.

12 Feigenbaum H. *Echocardiography*. 3rd ed. Philadelphia: Lea and Febiger, 1981:119–39.

13 Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. *Circulation* 1980;62:1054–61.

14 Sokal RR, Rolft FJ. *Biometry*. San Francisco: WH Freeman, 1969:2–5.

15 Maron BJ, Spirito P, Wesley Y, Arce J. Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy. *N Engl J Med* 1986;315:610–4.

Br Heart J 1987;58:267–73

Cross sectional subcostal echocardiography: atrioventricular septal defects and the short axis cut

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SUMMARY A short axis echocardiographic cut of the heart from the subcostal approach was used to study the atrioventricular junction in 47 infants and children with congenital heart disease and 20 with normal hearts. Examination of the diastolic openings of both atrioventricular valves was able to establish normal developments of the valves and annuli even when this was found in cases of complex congenital heart disease. In 30 patients with atrioventricular septal defects the technique distinguished between a partial defect (when the two atrioventricular valves were linked transseptally) and a complete defect (when there was only one atrioventricular valve). A range of atrioventricular attachments was seen in these patients.

Short axis echocardiography from the subcostal approach reliably identifies different forms of atrioventricular septal defects by defining the anatomy of the atrioventricular valves during maximal diastolic expansion.

The echocardiographic evaluation of atrioventricular septal defects[1] was initially carried out by M mode echocardiography.[2-4] Cross sectional echocardiography, however, gives more information and is more accurate.[5-7]

There has been extensive anatomical analysis of the different forms of this cardiac malformation.[8-10] This information[11-13] has led to an understanding of the echocardiographic features of the lesion,[14 15] but identification of the different types of atrioventricular septal defect continues to be difficult.[16-18]

In hearts with an atrioventricular septal defect both atrioventricular valves may be attached to the interventricular septum at the same level, forming two valves and two annuli, or there may be a single atrioventricular valve with one annulus common to both atria and both ventricles. It is possible to identify these two forms by examining the attachment of the atrioventricular valve(s) to the septum in a four chamber view.[19] There are, however, intermediate forms of the lesion in which the leaflets of a common atrioventricular valve are tethered to the septum.[20] Sutherland *et al*[21] and Medina *et al*[22] used M mode echocardiography from the subcostal approach in an attempt to improve identification of the intermediate forms. The M mode echocardiogram gave only a limited display of the cardiac anatomy that was difficult to understand.

We have used cross sectional short axis cuts of the heart at the level of the atrioventricular junction to examine more accurately the normal atrioventricular valve structures and to identify various forms of atrioventricular septal defect.

ECHOCARDIOGRAPHIC ANATOMY

The understanding of cardiac anatomy from cross sectional echocardiography is based on anatomical identification of different cardiac cuts from pathological specimens.[19 23] In normal hearts the cross sectional short axis view at the level of the atrioventricular valves shows two independent and well formed atrioventricular annuli with valves anchored to the left and right lateral heart walls as well as to the anteriorsuperior and posteriorinferior walls. The atrioventricular septum supports the septal leaflets of both atrioventricular valves (fig 1). The form of the atrioventricular valves and leaflets is best dis-

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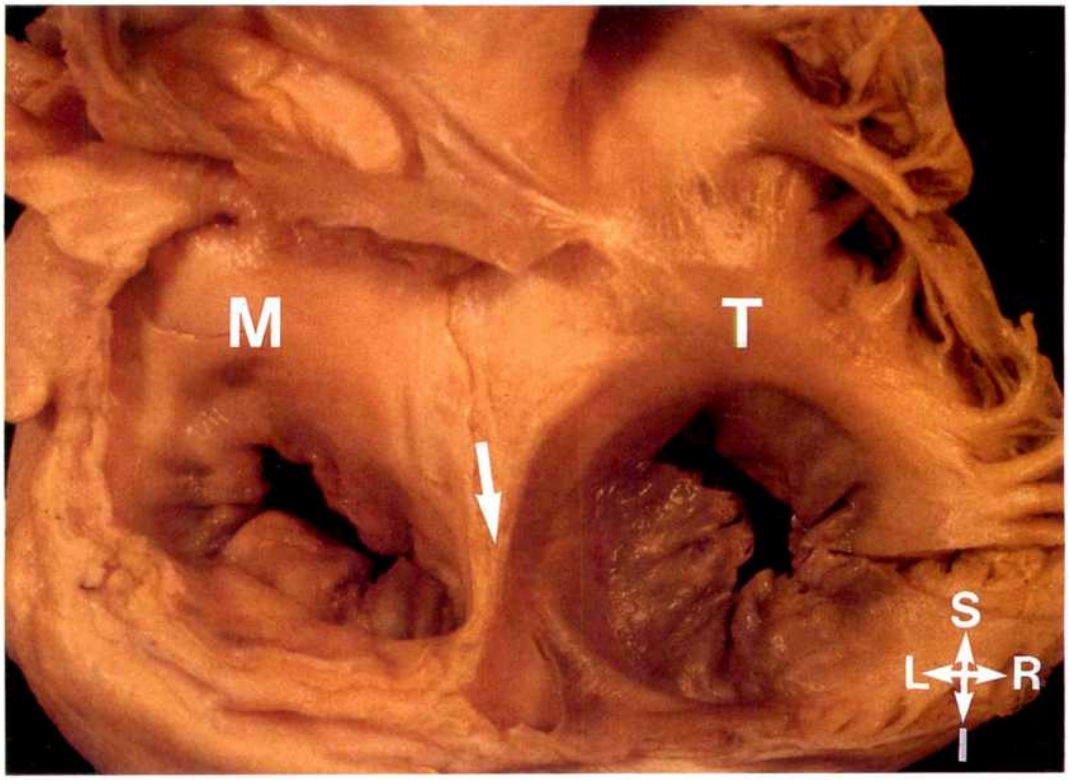

Fig 1 *Normal heart cut at the level of both atrioventricular valves. The atria have been removed and the tricuspid (T) and the mitral (M) valves are seen from above. The arrow indicates the superior part of the atrioventricular septum that separates both atrioventricular valves. I, inferior; L, left; R, right; S, superior.*

played during diastole, when extension of the valve components is greatest (fig 2).

In hearts with atrioventricular septal defects, either partial or complete, separate insertion of the two atrioventricular valves on to the septum is impossible. This is true of the two valves that are present in partial intraventricular septal defect or the one valve that is common to the four chambers of the heart when the defect is complete. The crest of the defective interventricular septum cannot adequately support the septal leaflets of the atrioventricular valves, and their insertion below the level of attachment of the valve leaflets in the lateral walls distorts the atrioventricular rings. In the partial form there are two atrioventricular valves and the anteriorsuperior and posterior or inferior septal components of the mitral and tricuspid valves are joined over the ventricular septum. The septal leaflets cover the crest of the interventricular septum with valve tissue to a variable degree (fig 3). In the complete form a single atrioventricular valve has an annulus that is common to both atria and both ventricles. The septal components of the common valve bridging the septum can be identified by a study of the variable number of chordal attachments and the different degrees to which the leaflets bridge the septum. At its centre the crest of the septum is free of valve tissue; there is a gap between the anterior-superior and posteriorinferior leaflets of the common valve (fig 4). In the intermediate form the crest of the interventricular septum is partially covered to a varying extent with valve tissue.

Patients and methods

Sixty seven patients aged one day to 12·5 years (mean age of 3·2 years) were studied by clinical examination, electrocardiography, chest x ray, and echocardiography (M mode, cross sectional imaging, and pulsed Doppler ultrasound). An atrioventricular defect was diagnosed in 30 patients. In six this was partial, in 21 it was complete, and in three it was regarded as intermediate. In six patients anatomical confirmation of the lesion was obtained

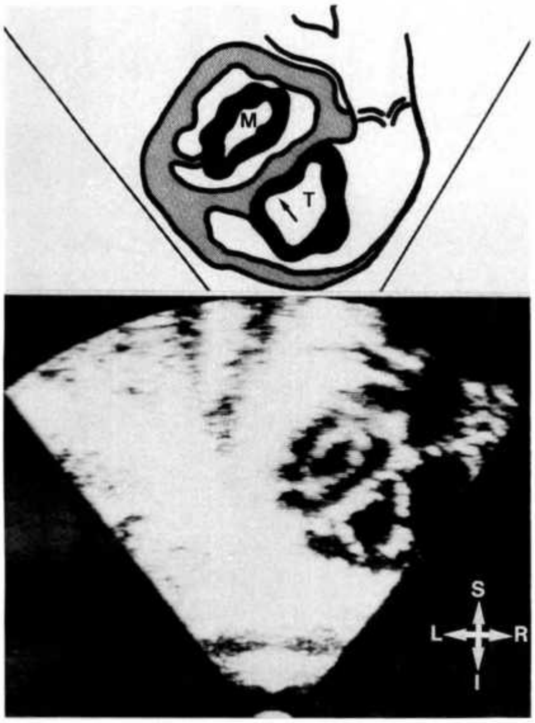

Fig 2 *Echocardiogram obtained from the subcostal approach in a child with a normal heart. Transversal short axis cut shows two independent atrioventricular valves at maximum aperture during diastole. The excursion of the septal leaflet of the tricuspid valve (T) opening is limited by the septum (arrow), whereas maximum excursion of the septal leaflet of the mitral valve (M) does not take it within reach of the septum. See legend to fig 1 for abbreviations.*

at cardiac catheterisation, angiography, and operation. In a further four patients diagnosis was confirmed by cardiac catheterisation only and in three by necropsy only. We also studied 20 normal children with innocent murmurs and 17 children with complex congenital heart disease. Anatomical confirmation of diagnosis in those with complex congenital heart disease was established by cardiac catheterisation in all and by necropsy in some.

For echocardiography we used a Honeywell Ultraimager machine equipped with a strip chart recorder and video system that allowed frame selection for evaluation of the anatomical data. We used 3·5 or 5 MHz transducers according to the patient's size and the best definition. We used pulsed Doppler ultrasound to assess function. In all patients the following echocardiographic views were imaged.

(*a*) *Parasternal approach*—long axis, short axis at different levels, and apical four chamber.

(*b*) *Subcostal approach*—short axis at atrial level, atrioventricular junction, and ventricular level. Subcostal short axis cuts (fig 5) were obtained by scanning from the ventricles to the atria. Valve anatomy was studied at a level at which the valve leaflets appeared to be separate from the chamber walls.

Results

Group 1—In the 20 patients with innocent murmurs who clinically and by other means had a normal heart subcostal echocardiography showed two valve orifices at the atrioventricular junction at maximal diastolic opening. These two orifices were separated by the interventricular septum. Part of the tricuspid valve lay in close apposition to the septum and during diastolic opening the orifice expanded to the right. The orifice of the mitral valve on the other hand lay well away from the septum (fig 2).

Group 2—In 17 patients echocardiographic examination confirmed complex congenital heart disease in patients who had an apparently normally developed atrioventricular junction and valve rings. The echocardiographic appearance of the atrioventricular openings was normal. This result was confirmed by cardiac catheterisation and necropsy.

Group 3—In 30 patients echocardiographic examination showed an atrioventricular septal defect. Six of these patients had a partial defect—the so-called ostium primum lesion. Subcostal echocardiography showed two atrioventricular valves that were continuous with each other over the crest of the interventricular septum (fig 6). All six patients had an ostium primum septal defect. Three had an additional small ventricular septal defect outside the inlet portion of the septum. A further 21 patients had a complete atrioseptal defect. Echocardiography identified only one atrioventricular valve common to both atria and ventricles. Anteriorsuperior and posteriorinferior bridging leaflets crossed the septum and with the lateral valve leaflets formed a single valve and a common orifice (fig 7).

Valve tissue was attached to varying extents to the crest of the interventricular septum; whenever one of the septal leaflets clearly bridged the septum (fig 8) a single atrioventricular valve and annulus was present. The degree of approximation between the septum and the valve leaflets varied. With complete defects there was always a gap in the attachments of the valve tissue to the septum. In three cases the echocardiogram suggested the presence of an intermediate form (fig 8). This was confirmed in one case at operation.

After surgical correction in the complete form, the two newly created valve orifices could be identified.

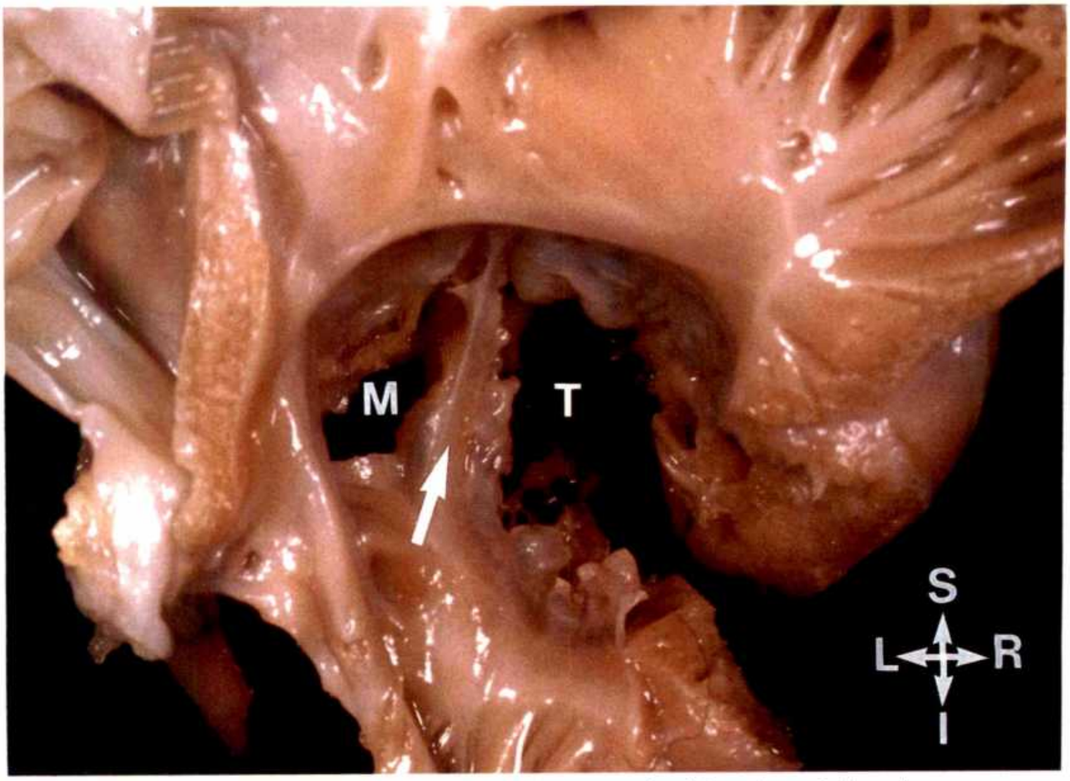

Fig 3 *Heart with an ostium primum defect. The atria have been removed and the atrioventricular valves are seen from above. There are two valve orifices. The septal leaflets of the tricuspid and mitral valves join over the septum (arrow). See legend to fig 1 for abbreviations.*

In the partial form the changes were not so pronounced and were obvious only when the gap between the septal bridging leaflets at the mitral end had been repaired.

Discussion

Atrioventricular septal defects result from a maldevelopment of the atrioventricular septum and atrioventricular valves.[9 11] Cross sectional echocardiography is the best non-invasive way to study the atrioventricular junction.[6 19] Recent studies have demonstrated the correlation between the distorted cardiac anatomy found in these hearts and the echocardiographic images.[14] Furthermore, the subcostal approach appears to be the best method of studying the atrioventricular junction.[21 22] In this group of patients the short axis view from the subcostal approach was found to be the most valuable echocardiographic plane for evaluating the annuli and the atrioventricular valves.

Most of the echocardiographic studies of atrioventricular septal defects have based their anatomical understanding of this lesion on schematic diagrams of the arrangement at the level of the atrioventricular valve. Moreover, heart specimens very rarely have been cut in the short axis plane to illustrate the range and degree of valve anomaly seen in atrioventricular septal defects (figs 1, 3, and 4). The four chamber view has usually been used to evaluate this lesion.

The four chamber view from the subcostal or parasternal approach is likely to detect the presence of a defect under the anterior or posterior bridging leaflet that may be only apparent in systole. But the short axis view in diastole, however, will be more sensitive to defects in the atrioventricular valves. Another limitation of the four chamber view is its inability to visualise simultaneously the anterior and posterior valve components.

We found that the short axis subcostal approach clearly demonstrated the two atrioventricular valves and normal valve anatomy even in patients with complex congenital cardiac malformation of other areas of the heart.

Our echocardiographic evaluation was performed

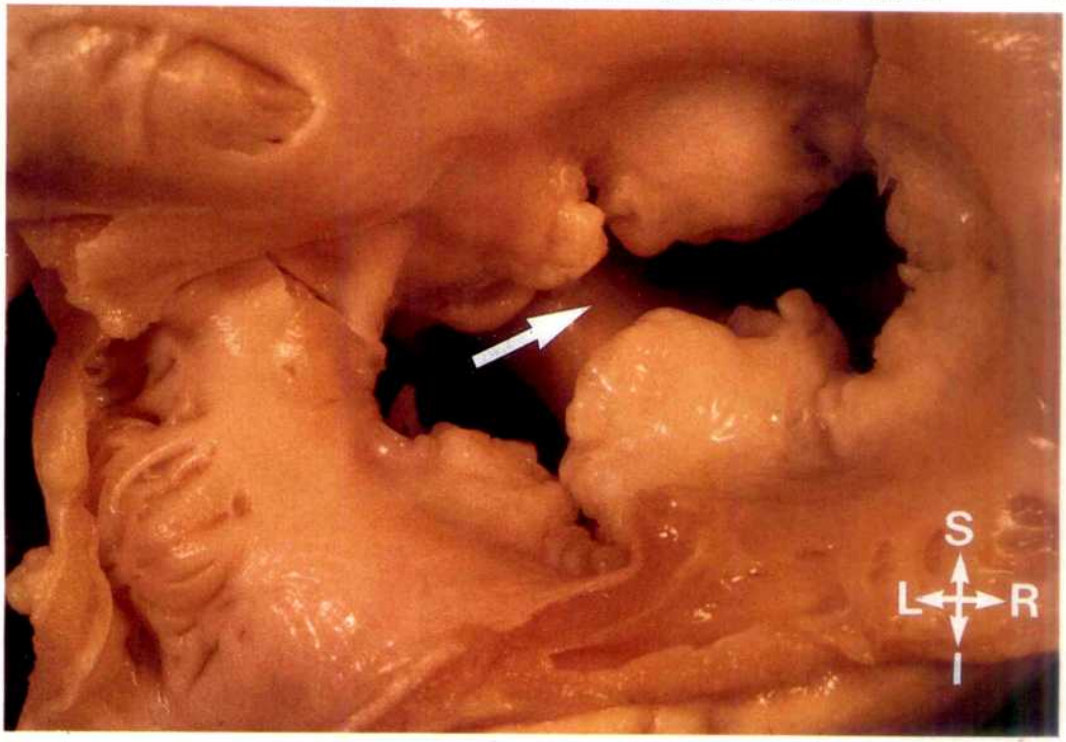

Fig 4 *Heart with a complete atrioventricular septal defect. Only one valve and one annulus are seen from above. The anterosuperior and posteroinferior septal components are not fused. The crest of the interventricular septum is seen underneath. See legend to fig 1 for abbreviations.*

during diastole when the valve tissue was widely separated and the two atrioventricular valve contours could be seen entirely. In normal patients two annuli were easily identified. At maximum diastolic aperture the anterior leaflet of the mitral valve was clearly separated from the septum and a well defined circle was formed. In contrast, the orifice of the tricuspid valve was limited by the interventricular septum (fig 2).

We found that valve anatomy was quite different in patients with atrioventricular septal defects. With a partial defect the two annuli were joined over the interventricular septum. Neither valve had a circular orifice; both were oval because of the attachment of the bridging leaflets to the crest of the interventricular septum (fig 6). When the defect was complete there was a large atrioventricular valve orifice that was common to both atria and both ventricles. Because there was no coaptation of the septal components in the middle of what should be the mitral and tricuspid valves a common valve orifice was formed (fig 7). The valve contours represented the septal leaflets of both valves which formed a continuous bridge over the interventricular septum. In

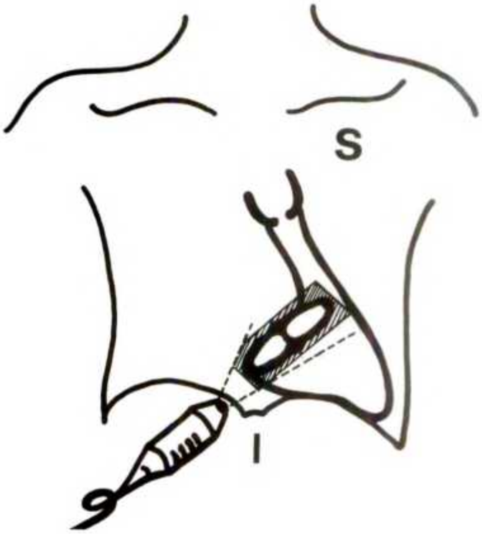

Fig 5 *Diagram to show the transducer orientation from the subcostal approach.*

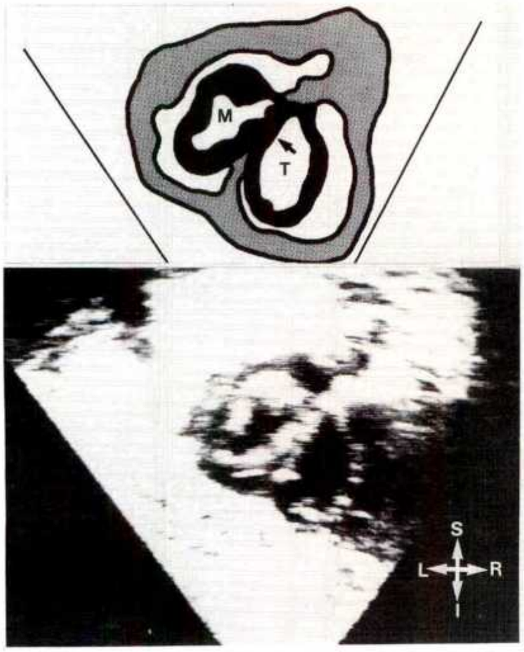

Fig 6 *Echocardiogram of an ostium primum defect. Two valve orifices were seen at their maximum expansion. The septal leaflets of both valves were fused over the septum (arrow). See legend to fig 1 for abbreviations.*

some cases one of the leaflets was anchored to the crest of the septum but there was a gap between the valve and septum (fig 8) and only one valve was present. Surgical correction created a more normal arrangement of the atrioventricular valves with the formation of two valve rings; however, the valves lay abnormally close to the septum.

We found that the short axis cut from the subcostal approach clearly displayed normal anatomy of atrioventricular valves even when this was found in cases of complex congenital heart disease. The technique discriminated between partial (two atrioventricular orifices) and complete (one orifice) atrioventricular septal defects and showed the degree of apposition between the anteriorsuperior and posteriorsuperior leaflets of the atrioventricular valve. The degree of attachment of valve tissue to the crest of the septum could also be visualised. This view was usually more helpful than the four chamber view for reliably identifying the various forms of the defect. In the intermediate form of the defect two valves are almost formed but a small degree of separation of the septal cusp tissue remains. These specimens resemble a partial form but there is a small gap in the valve tissue. When the full contours of the valves are imaged the three forms can be identified reliably. A short axis cut at atrial level may be misleading if part of the ostium primum defect is taken to be the orifice of the valve. In this situation the valve tissue contours must be imaged before the type of defect can be identified.

The precise definition of the anatomy of the atrioventricular valve by echocardiography makes it possible to establish the diagnosis of this malformation and allows evaluation of the degree of valve distortion—this is important information when surgical correction is planned. The only limitation of the approach is the difficulty of seeing the heart from the subcostal axis. This route is suitable for small children but less so for adults.

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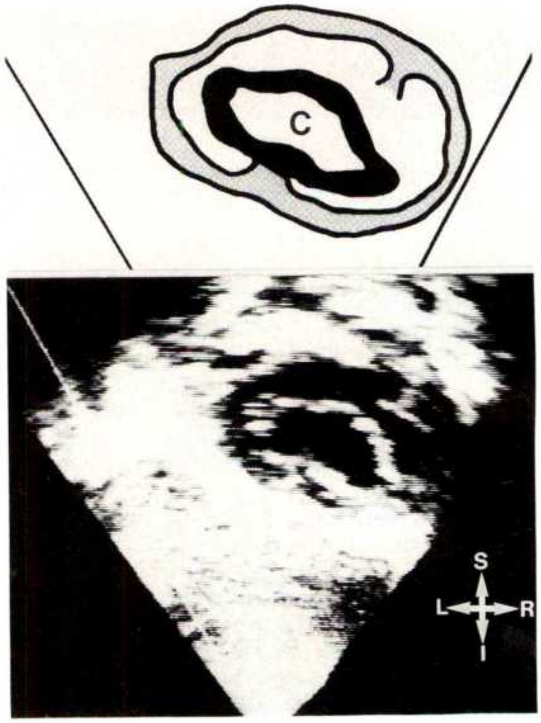

Fig 7 *Echocardiogram from a patient with a complete atrioventricular defect. Only one valve was seen at diastolic maximum aperture. This was common to all four chambers. The components of the septal valves were not fused in the middle as they were in the partial form. They formed a continuous bridge over the septum and so there was one valve ring. C, common valve. See legend to fig 1 for abbreviations.*

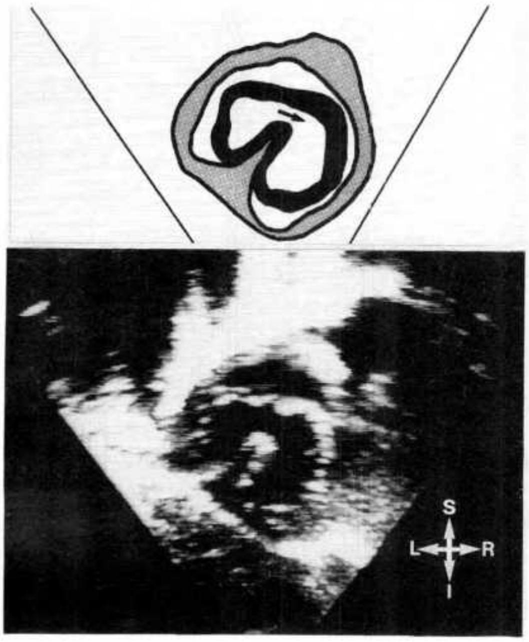

Fig 8 *Echocardiogram from a patient with an intermediate form of atrioventricular septal defect. The components of the septal valves were not fused (arrow). Only the anterosuperior valve leaflet bridged the septum and was common to both ventricles and atria. The posteroinferior septal component was anchored to the crest of the septum and partly separated both valve orifices.*

References

1 Williams RG, Rudd M. Echocardiographic features of endocardial cushion defects. *Circulation* 1974;**49**: 418–22.

2 Pieroni DR, Homcy E, Freedom RM. Echocardiography in atrioventricular canal defect: a clinical spectrum. *Am J Cardiol* 1975;**35**:54–8.

3 Komatsu Y, Nagai Y, Shibuya M, Takao A, Hirosawa K. Echocardiographic analysis of intracardiac anatomy in endocardial cushion defect. *Am Heart J* 1976;**91**:210–8.

4 Beppu S, Nimura Y, Nagata S, *et al*. Diagnosis of endocardial cushion defect with cross-sectional and M-mode scanning echocardiography. Differentiation from secundum atrial septal defect. *Br Heart J* 1976;**38**:911–20.

5 Sahn DJ, Terry RW, O'Rourke R, Leopold G, Friedman WF. Multiple crystal echocardiographic evaluation of endocardial cushion defect. *Circulation* 1974;**50**:25–32.

6 Hagler DJ, Tajik AJ, Seward JB, Mair DD, Ritter DG. Real-time wide angle sector echocardiography: atrioventricular canal defects. *Circulation* 1979;**59**: 140–50.

7 Seward B, Tajik AJ, Hagler DJ. Two-dimensional echocardiographic features of atrioventricular canal defect. In: Lundström NR, ed. *Pediatric echocardiography-cross-sectional, M-mode, and Doppler*. Amsterdam: Elsevier/North Holand, 1980:197–206.

8 Campbell M, Missen GAK. Endocardial cushion defects: common atrio-ventricular canal and ostium primum. *Br Heart J* 1957;**19**:403–18.

9 Rastelli G, Kirklin JW, Titus JL. Anatomic observations on complete form of persistent common atrioventricular canal with special reference to atrioventricular valves. *Mayo Clin Proc* 1966;**41**:296–308.

10 Bharati S, Lev M. The spectrum of common atrioventricular orifice (canal). *Am Heart J* 1973;**83**: 553–61.

11 Ugarte M, Enriquez de Salamanca F, Quero M. Endocardial cushion defects. An anatomical study of 54 specimens. *Br Heart J* 1976;**38**:674–82.

12 Piccoli GP, Gerlis LM, Wilkinson JL, Lozsadi K, Macartney FJ, Anderson RH. Morphology and classification of atrioventricular defects. *Br Heart J* 1979;**42**:621–32.

13 Piccoli GP, Wilkinson JL, Macartney FJ, Gerlis LM, Anderson RH. Morphology and classification of complete atrioventricular defects. *Br Heart J* 1979;**42**:633–9.

14 Smallhorn JF, Tommasini G, Anderson RH, Macartney FJ. Assessment of atrioventricular septal defects by two dimensional echocardiography. *Br Heart J* 1982;**47**:109–21.

15 Gussenhoven EJ, Becker AE. *Congenital heart disease. Morphologic echocardiographic correlations*. Amsterdam: Churchill Livingstone, 1983:102–17.

16 Hagler DJ. *Atrioventricular canal defects*. Philadelphia: WB Saunders, 1976:87–109.

17 Bass JL, Bessurger FB, Lawrence C. Echocardiographic differentiation of partial and complete atrioventricular canal. *Circulation* 1978;**57**:1144–50.

18 Mortera C. Echocardiography of atrioventricular canal malformations. In: Lundström NR, ed. *Pediatric echocardiography-cross-sectional, M-mode, and Doppler*. Amsterdam: Elsevier/North Holland, 1980: 187–96.

19 Seward JB, Tajik AJ, Hagler DJ, Edwards WD. Internal cardiac crux: two dimensional echocardiography of normal and congenitally abnormal hearts. *Ultrasound Med Biol* 1984;**10**:735–45.

20 Bharati S, Lev M, McAllister HA, Kirklin JW. Surgical anatomy of the atrioventricular valve in the intermediate type of common atrioventricular orifice. *J Thorac Cardiovasc Surg* 1980;**79**:884–9.

21 Sutherland GR, Van Mill GJ, Anderson RH, Hunter S. Subxiphoid echocardiography—a new approach to the diagnosis and differentiation of atrioventricular defects. *Eur Heart J* 1980;**1**:45–55.

22 Medina Fernandez A, Bethencourt Gonzalez A, Macaya Miguel C, Tynan M, Anderson RH. Subxiphoid M-mode echocardiography in atrioventricular defects. *Pediatr Cardiol* 1982;**3**:119–25.

23 Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two-dimensional realtime ultrasonic imaging of the heart and great vessels. Technique, image, orientation, structure identification and validation. *Mayo Clin Proc* 1978;**53**:271–303.

Br Heart J 1987;**58**:274–8

Interrupted right aortic arch in DiGeorge syndrome

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SUMMARY The clinical and necropsy findings in four cases of interrupted right aortic arch and right descending aorta associated with DiGeorge syndrome (congenital absence or hypoplasia of the thymus and parathyroids) are described. All patients had a mirror image of type B interruption, namely a right aortic arch with reversed branching pattern and an interruption between the right common carotid and right subclavian artery. In two patients there was a doubly committed subarterial ventricular septal defect and in the two other patients there was a perimembranous septal defect. Three patients had a bicuspid aortic valve. In a consecutive series of 185 necropsies in infants and children with congenital heart disease there were no cases of interrupted right aortic arch that were not associated with DiGeorge syndrome.

These observations and previous reports indicate that the concurrence of these two rare conditions is more than fortuitous. In patients with an interrupted aortic arch the clinician should be aware of the common association with DiGeorge syndrome. If the interruption is associated with a right-sided descending aorta it is highly probable that the patient has DiGeorge syndrome.

Interruption of the aortic arch is an uncommon cardiovascular anomaly which is almost invariably associated with a left-sided descending aorta, continuous with a left ductus arteriosus.[1-3] There are only a few recorded cases of interruption associated with a right-sided aortic arch.[3-6] We found this anatomical arrangement in four patients seen during the past ten years. In all four patients the thymus was absent, hypoplastic, or ectopic, as is characteristically seen in DiGeorge syndrome.[7] The concurrence of these two rare conditions is more than fortuitous and is therefore reported.

Patients and methods

Nineteen cases with absence or hypoplasia of the thymus were found in a consecutive series (June 1976 to October 1986) of 185 necropsies in infants and children with congenital heart disease. All patients had major cardiovascular malformations (table 1). Twelve patients had an interrupted aortic arch, which was left-sided in eight cases and right-sided in four cases. This paper deals with the findings in the four patients with an interrupted aortic arch and a right-sided descending aorta, two of whom (cases 1 and 2) were mentioned in a previous report.[5] Apart from these four patients no other cases of interrupted right aortic arch could be traced from our necropsy or clinical files.

Agenesis and hypoplasia of the thymus were defined as total or partial developmental absence of the gland respectively. Stress involution was distinguished from hypoplasia because it caused sym-

Table 1 *Major cardiovascular malformations in 19 patients with DiGeorge syndrome*

Malformation	*No*
Interrupted aortic arch:	
Left aortic arch	8
Right aortic arch	4
Truncus arteriosus:	
Left aortic arch	3
Right aortic arch	2
Tetralogy of Fallot:	
Right aortic arch	2
Total	19

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metrical shrinkage and the persistence of the normal bilobed anatomy. In three of the four patients the tissue of the anterosuperior mediastinum and cervical region, which had been removed en bloc, was serially sectioned at 5 μm, and every tenth section was stained and histologically examined. By analogy with the classification proposed by Celoria and Patton[1] we used the term "type B interruption" of the aortic arch when the interruption was situated between the right common carotid artery and the right subclavian artery. Ventricular septal defects were classified according to Becker and Anderson.[8]

Results

CLINICAL DATA

All four patients were admitted in the first weeks of life with severe and intractable congestive heart failure. They died at 2, 12, 16, and 17 days of age. The concentration of serum calcium was normal in the two patients (cases 2 and 3) in whom it was measured. Craniofacial stigmata characterised by low-set ears, ocular hypertelorism, retrognathia, and a fish-mouth appearance were seen in cases 3 and 4.

Cardiac catheterisation and angiocardiography were performed in three patients (cases 1, 2, and 4). Considerable pulmonary hypertension, equal pressures in the right and left ventricles, and a large left-to-right shunt at the ventricular level were demonstrated. The systolic pressure in the right-sided descending aorta, which in all three patients could easily be entered from the pulmonary artery via a right-sided ductus arteriosus, was slightly lower than in the ventricles. The angiograms showed the characteristic features of interruption of the aortic arch, which will be discussed in more detail (fig 1).

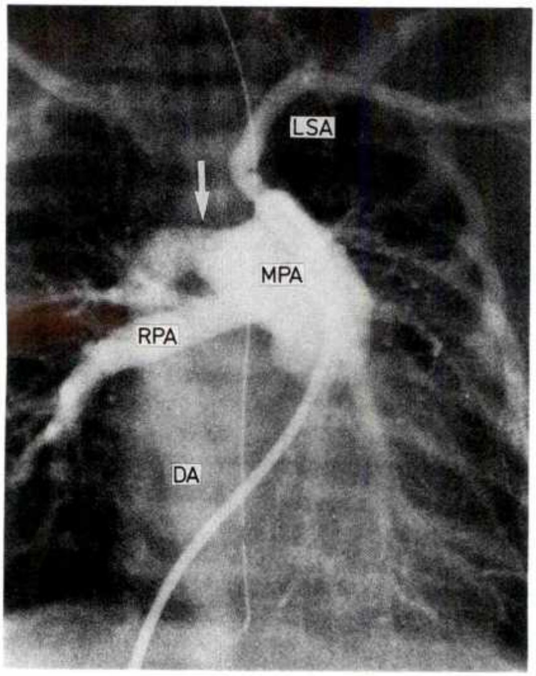

Fig 1 *Angiogram in case 2 showing filling of the pulmonary artery and a bilateral ductus arteriosus. A right-sided descending aorta communicated with the pulmonary artery through a large right ductus arteriosus (white arrow). The left subclavian artery filled through a left ductus arteriosus. DA, descending aorta; LSA, left subclavian artery; MPA, main pulmonary artery; RPA, right pulmonary artery.*

CARDIOVASCULAR ANOMALIES

Table 2 shows the major cardiovascular findings at necropsy. In each of the four cases the interruption of the aortic arch was type B. The descending aorta was located to the right of the oesophagus and was supplied by a right ductus arteriosus arising from the pulmonary trunk. The right subclavian artery arose from the superior aspect of the descending aorta. In cases 1, 3, and 4 the first branch of the ascending aorta was the left innominate artery, which gave rise to the left subclavian and the left common carotid artery; the right common carotid artery was the second branch (fig 2). In case 2 the ascending aorta gave rise only to the left and right common carotid arteries (fig 3). In this exceptional case a bilateral ductus arteriosus was identified. The left subclavian artery was isolated from the aortic arch and connected with the pulmonary trunk via a left ductus arteriosus. The right ductus arteriosus supplied the descending aorta.

In cases 1 and 2 a doubly committed subarterial ventricular septal defect was found. This defect was located directly beneath the aortic and pulmonary valves and its floor was formed by the fused portions of the trabecula septomarginalis and the ventriculoinfundibular fold (fig 4). In the remaining two patients with perimembranous ventricular septal defect the infundibulum was slightly deviated to the left, causing some muscular subaortic stenosis. Patients 1, 2, and 4 had a bicuspid aortic valve.

THYMUS AND PARATHYROIDS

In two patients (cases 3 and 4) rudimentary fragments of the thymus could be identified macroscopically. Serial histological examination of the cervical and mediastinal tissue showed small thymic remnants in the remaining two patients. The histological structure of this thymic tissue was normal. Evidence of involution was slight to moderate. After serial sectioning and histological examination of the anterior mediastinum and neck, two normal para-

Table 2 *Pathological findings*

Patient No	*Sex*	*Age at death*	*Thymus*	*Parathyroids*	*Type of AoA interruption*	*VSD*	*Other cardiovascular anomalies*
1	F	12 days	Absent. Small nodule (7 mm) in R upper mediastinum	Not examined	B	Doubly committed subarterial	Bicuspid AoV
2	F	16 days	Absent. Tiny nodule along R carotid (0·4 g)	2 normal R glands. L gland absent	B	Doubly committed subarterial	Bicuspid AoV. Bilateral PDA. L subclavian artery connecting with L PDA
3	F	2 days	Absent L lobe. Small R lobe (2·7 g) in R upper mediastinum	2 hypoplastic glands	B	Perimembranous infundibular	None
4	F	17 days	Absent R lobe. Small L lobe (1·6 g) in L upper mediastinum	Absent	B	Perimembranous infundibular	Bicuspid AoV. L shift of CSV and subaortic encroachment

AoA, aortic arch; AoV, aortic valve; CSV, crista supraventricularis; L, left; R, right; PDA, ductus arteriosus; VSD, ventricular septal defect.

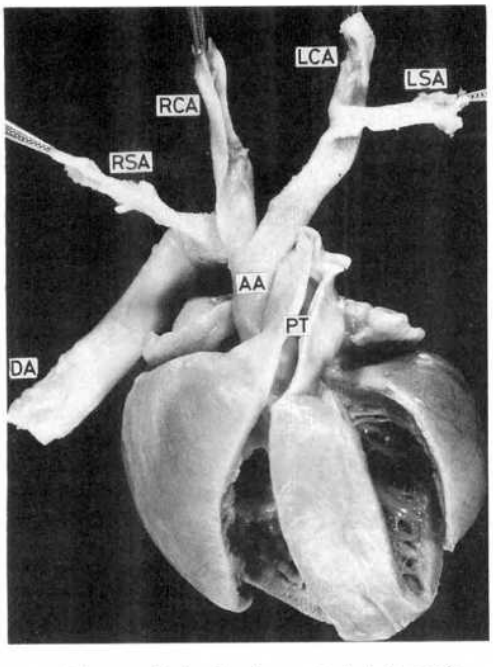

Fig 2 *Photograph showing interrupted right aortic arch type B in case 3. The right-sided descending aorta communicated with the pulmonary artery through a wide right ductus arteriosus. AA, ascending aorta, DA, descending aorta, LCA, left common carotid artery, LSA, left subclavian artery; RCA, right common carotid artery; RSA, right subclavian artery; PT, pulmonary trunk.*

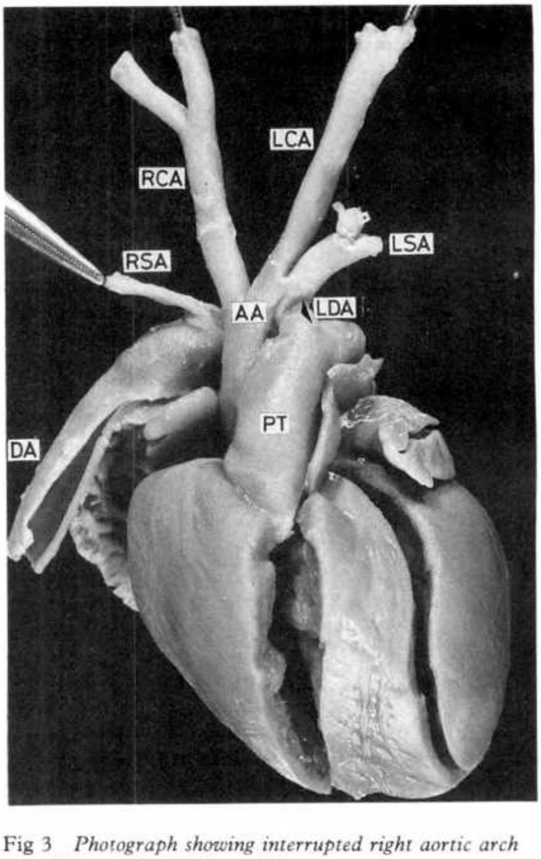

Fig 3 *Photograph showing interrupted right aortic arch type B in case 2. A bilateral ductus arteriosus was identified. The left subclavian artery was isolated from the aortic arch and connected to the pulmonary trunk via a left ductus arteriosus (LDA). The right ductus arteriosus supplied the descending aorta. See fig 2 for abbreviations.*

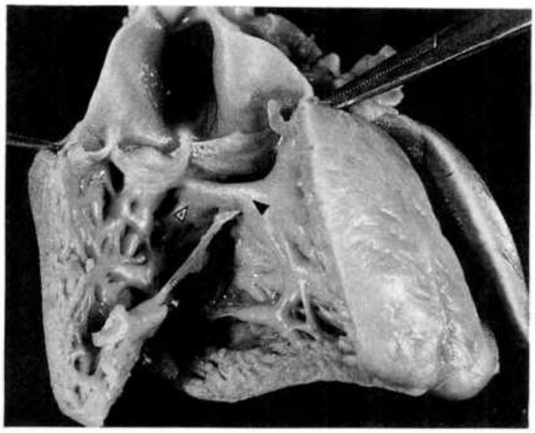

Fig 4 *Photograph showing doubly committed subarterial ventricular septal defect in case 1. In the opened right ventricle the defect was seen directly beneath the pulmonary valve. Its floor was formed by the fused portions of the trabecula septomarginalis (closed arrow) and the ventriculoinfundibular fold (open arrow).*

thyroid glands were detected in case 2, two hypoplastic glands in case 3, and no parathyroids in case 4. When present, the glandular tissue showed a normal histological structure.

Discussion

DiGeorge syndrome is a complex of malformations of unknown aetiology that is generally attributed to failure of the development of derivatives of the third and fourth pharyngeal pouches. The essential features are congenital absence or hypoplasia of the thymus and parathyroid glands. The extent of the underdevelopment of these organs and the corresponding variation in the degrees of deficient cellular immunity and hypocalcaemia led to a classification in which partial and complete forms of the syndrome are distinguished.[7] Facial stigmata, characterised by ocular hypertelorism, narrow palpebral fissures, a fish-mouth appearance, micrognathia, and deformed ear lobes are seen in more than half the cases.[5 9] Severe cardiovascular malformations are found in nearly all patients with either the complete or partial form of the syndrome.[5 9–11] The vast majority of these malformations may be classified as aortic arch anomalies (right aortic arch, interrupted aortic arch, aberrant origin of the subclavian arteries) or conotruncal anomalies (truncus arteriosus, tetralogy).

DiGeorge syndrome is not as rare as generally thought. The fact that we found 19 patients with complete or partial absence of the thymus in a series of 185 infants and children with congenital heart disease who came to necropsy within a 10 year period may be due to the interest that the pathologists were taking in this syndrome and the attention they paid to the development of the thymus and parathyroid glands. Twelve of these 19 cases had interruption of the aortic arch, which was associated with a right-sided descending aorta and a right patent ductus arteriosus in four patients (table 1). No other cases of interrupted right aortic arch were encountered in this necropsy series nor in a patient population of approximately 5000 infants and children with congenital heart disease investigated during the same period. Thus we have not come across a single case of interrupted right aortic arch not associated with DiGeorge syndrome. Three additional patients in the necropsy series had a right-sided aortic arch and descending aorta, which was associated with truncus arteriosus in two and tetralogy of Fallot in one case. A high frequency of right aortic arch in DiGeorge syndrome (seven out of 19 cases in the present series) has also been noted by others: it was found in 42% of 52 cases compiled by Moerman *et al*[5] and in 24% of a series of 50 patients reported by Van Mierop and Kutsche.[11]

In view of the high frequency of right aortic arch and the equally high frequency of interrupted aortic arch in DiGeorge syndrome, it is not surprising that all three malformations were found in some patients. To our knowledge eight cases of interrupted right aortic arch have been reported. Pierpont *et al* described the pathological features in four cases but did not mention the anatomy of the thymus.[6] Nor was it mentioned in two other cases.[2 4] So we can only speculate about the presence of thymic aplasia or hypoplasia in these patients. In the remaining two patients,[11 12] however, and in the four patients in our series in whom the thymus was examined, the typical features of DiGeorge syndrome were found. Interruption of the aortic arch with right descending aorta may cause compression of the right main bronchus, resulting in severe lobar emphysema of the right lung.[6] This complication was not encountered in our patients.

Our observations support the concept that the basic developmental defect in DiGeorge syndrome affects the cephalic neural crest. Experimental studies have shown that normal aorticopulmonary septation and thymic morphogenesis depend on derivatives of the cephalic neural crest.[13–15] In early embryogenesis, mesenchymal cells from the neural crest also contribute to the connective tissue, bone, and cartilage of the face and branchial arches.[16] In DiGeorge syndrome an abnormal neural crest and abnormal migration of branchial arch mesenchymal tissue probably result in an abnormal facies, partial or complete absence of the derivatives of the third and fourth pharyngeal pouches (thymus and parathyroid glands), and conotruncal cardiac defects. The aortic arch anomalies that are found in many of these patients might be secondary to conotruncal maldevelopment causing reduced anterograde blood flow in the ascending aorta and impeded normal growth of the aorta.[17] Recently, Lammer *et al* suggested that the deficient activity and migration of cephalic neural crest cells might be related to vitamin A teratogenicity.[18]

DiGeorge syndrome is rarely diagnosed before operation or necropsy. This may be because hypocalcaemia is not often the presenting feature and abnormal susceptibility to infections only becomes obvious in the first months of life in the few patients who have a normal heart or survive with a cardiovascular malformation. Clinical recognition is important if cardiac surgery is considered, because the transfusion of irradiated blood may avoid a serious graft versus host reaction.[11] The clinician should suspect DiGeorge syndrome in infants with interruption of the aortic arch or truncus arteriosus, particularly if they have facial stigmata and hypocalcaemia. Our study indicates that the degree of suspicion should be even higher if the interruption of the aortic arch is associated with a right-sided descending aorta.

References

1 Celoria G, Patton R. Congenital absence of the aortic arch. *Am Heart J* 1959;58:407–13.

2 Van Praagh R, Bernhard WF, Rosenthal A, Parisi LF, Fyler DC. Interrupted aortic arch: surgical treatment. *Am J Cardiol* 1971;27:200–11.

3 Van Mierop LH, Kutsche LM. Interruption of the aortic arch and coarctation of the aorta: pathogenetic relations. *Am J Cardiol* 1984;54:829–34.

4 Kleinerman J, Yang WM, Hackel DB, Kaufman N. Absence of the transverse aortic arch. *Arch Pathol* 1958;65:490–8.

5 Moerman P, Goddeeris P, Lauweryns J, Van der Hauwaert LG. Cardiovascular malformations in DiGeorge syndrome (congenital absence or hypoplasia of the thymus). *Br Heart J* 1980;44:452–9.

6 Pierpont ME, Zollikofer CL, Moller JH, Edwards JE. Interruption of the aortic arch with right descending aorta. A rare condition and a cause of bronchial compression. *Pediatr Cardiol* 1982;2:153–9.

7 Lischner H. DiGeorge syndrome(s). *J Pediatr* 1972;81: 1042–4.

8 Becker AE, Anderson RH. *Pathology of congenital heart disease*. London: Butterworths, 1981:93–117.

9 Freedom RM, Rosen FS, Nadas AS. Congenital cardiovascular disease and anomalies of the third and fourth pharyngeal pouch. *Circulation* 1972; 46:165–72.

10 Conley ME, Beckwith JB, Mancer JF, Tenckhoff L. The spectrum of the DiGeorge syndrome. *J Pediatr* 1979;94:883–90.

11 Van Mierop LH, Kutsche LM. Cardiovascular anomalies in DiGeorge syndrome and importance of neural crest as a possible pathogenetic factor. *Am J Cardiol* 1986;58:133–7.

12 Duncan WJ, Tyrrell MJ, Bharadwaj B, Rosenberg AM, Schroeder ML, Bingham WT. Complex transposition with interrupted right aortic arch and partial DiGeorge syndrome. *Pediatr Cardiol* 1984;5:217–20.

13 Kirby ML, Gale TF, Stewart DE. Neural crest cells contribute to normal aorticopulmonary septation. *Science* 1983;220:1059–61.

14 Bockman DE, Kirby ML. Dependence of thymus development on derivatives of the neural crest. *Science* 1984;223:498–500.

15 Clark EB, Hu N, Rosenquist GC. Effect of conotruncal constriction on aortic-mitral valve continuity in the stage 18, 21 and 24 chick embryo. *Am J Cardiol* 1984;53:324–7.

16 Weston JA. The migration on differentiation of neural crest cells. *Advances in Morphology* 1970;8:41–114.

17 Robinson HB. DiGeorge's or the III-IV pharyngeal pouch syndrome. Pathology and a theory of pathogenesis. *Perspect Pediatr Pathol* 1975;2:173–206.

18 Lammer EJ, Chen DT, Hoar RM, *et al*. Retinoic acid embryopathy. *N Engl J Med* 1985;313:837–41.

Br Heart J 1987;58:279–83

Brucella endocarditis

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SUMMARY Brucella endocarditis is an underdiagnosed, fatal complication of human brucellosis. Four successfully treated cases of *Brucella* endocarditis are reported. The development of a new valvar lesion and bulky vegetations seen on echocardiography helped to identify *Brucella* endocarditis occurring during systemic brucellosis. The aortic valve was affected in all four patients, and in one the mitral valve was also affected. Medical treatment did not cure the patients and all needed valve replacement—for haemodynamic deterioration in three and because a further embolism was feared in one. Antibiotics were continued for six to nine months after operation. There was no early or late mortality and no recurrence after a follow up of 15 months.

Brucellosis is a very common disease; according to the World Health Organisation 500 000 new cases, mainly caused by *Brucella melitensis*, are reported annually.[1] The disease is underdiagnosed and underreported; some authorities estimate that for each case reported another 26 are not recognised or not reported.[2 3]

Human brucellosis is usually caused by one of three species of the genus Brucella: *melitensis*, *abortus*, and *suis*; it is rarely caused by *Brucella canis*.[3] Brucellae are small, non-motile, gram negative capnophilic coccobacilli with optimum growth at temperature of 37°C and a pH of 6·6–6·8. Brucellosis is found primarily in animals and is spread to man by direct contact with infected tissue or by ingestion of infected animal products, most commonly milk or milk products. In Western countries, brucellosis is an occupational disease found mainly in farmers, people working in meat packing plants, veterinary surgeons, and livestock producers. In other areas of the world the disease is more widespread and is found in the general population.

Cardiovascular complications of systemic brucellosis include endocarditis, myocarditis, and pericarditis, and these are the most common causes of death in brucellosis.[4–6]

There are only six reported cases of surgically cured *Brucella* endocarditis[7–12]; we report an additional four cases.

Patients and methods

Between January 1980 and January 1986 *Brucella* endocarditis was diagnosed in four patients referred to King Faisal Specialist Hospital. One of these patients has been the subject of an earlier report.[12] The diagnosis of endocarditis was established by the development of a new murmur and the presence of a vegetation on echocardiograms obtained during the course of systemic brucellosis, and was further supported by cardiac surgical findings and histopathology.

The following data were collected: symptoms at presentation, total and differential white blood cell count, erythrocyte sedimentation rate, electrocardiogram, serology, and blood culture. Serology included a Brucelloslide test (Bio Merienst) followed by a *Brucella* antibody tube dilution titre (Wellcome Diagnostics). Blood cultures were drawn and incubated in a supplemental yeast-peptone broth (Beckton-Dickinson). Initially kept in a vacuum, the cultures were exposed to air on day 7 and were thereafter incubated in an atmosphere of 5%–10% carbon dioxide. Subcultures on to blood agar plates were

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Table *Symptoms on admission*

	Patients			
	1	*2*	*3*	*4*
Age and sex	25 M	62 M	42 M	32 M
Ingestion of raw milk	+	+	+	+
Duration of fever	6 mth	2 mth	11 mth	4 mth
Malaise or weight loss	+	+	+	+
Night sweats	+	+	+	+
Dyspnoea	+	+	+	+
Functional class NYHA	IV	II	II	II
Embolic episodes	—	Coronary	CVA	—
Known heart disease	—	—	—	—

NYHA, New York Heart Association; CVA, cardiovascular accident.

made weekly and kept for four days. Surgical specimens were cultured in thioglycolate broth, and inoculated on to routine culture media. All cultures identified as possibly containing fastidious organisms were kept for six weeks. Cultures containing pale-staining Gram negative coccobacillary rods that were both oxidase-positive and urease-positive were identified as brucellae. *Brucella* titres were measured and blood cultures performed on all patients on admission, at operation, and every three months for a year. M mode and cross sectional echocardiography was performed on all patients and Doppler echocardiography on all except patient 1. Patients 1 and 2 had right and left cardiac catheterisation.

Results

SYMPTOMS (Table)

All four patients were men aged 25–62 (mean 40). Symptoms had appeared two to eleven months before admission. At the time of admission, one patient was in New York Heart Association class IV and three were in class II; two of the latter deteriorated to class IV. Two patients (cases 2 and 3) had systemic embolisation to the coronary and cerebral arteries respectively. No patient had a known history of valvar heart disease.

PHYSICAL SIGNS

All patients were febrile and all had splenomegaly; one patient had finger clubbing. The aortic valve was affected in all patients; in one the mitral valve was also affected. Patient 1 was admitted with aortic regurgitation and acute pulmonary oedema. Two patients (cases 2 and 4) developed sudden severe, aortic regurgitation while in hospital receiving treatment and acute pulmonary oedema developed.

INVESTIGATIONS

Three patients had a normal white cell count (4900–7600/mm^3) and one had leucopenia (2900/mm^3). The erythrocyte sedimentation rate was increased in three patients (range 56–85 mm/h) and was normal (6 mm/h) in one patient.

Electrocardiography showed sinus rhythm in all patients and none developed conduction disturbance. The patient with coronary embolism developed ventricular tachycardia and later ST-T wave changes.

Echocardiography showed a vegetation on the aortic valve in all patients; patient 4 had an additional vegetation on the mitral valve (fig 1). All vegetations were bulky, and in patient 3 the vegetation was pedunculated and prolapsing into the left ventricular outflow tract. Premature closure of the mitral valve indicative of acute aortic regurgitation was seen in patients 1, 2, and 4. Pulsed Doppler performed in the last three patients showed appreciable aortic regurgitation in all, with additional mitral regurgitation in one patient.

Serology showed a very high *Brucella* titre (range 2560–16 000) in all patients. Despite medical treatment all titres remained high or increased from the time of admission up to the time of operation (fig 2).

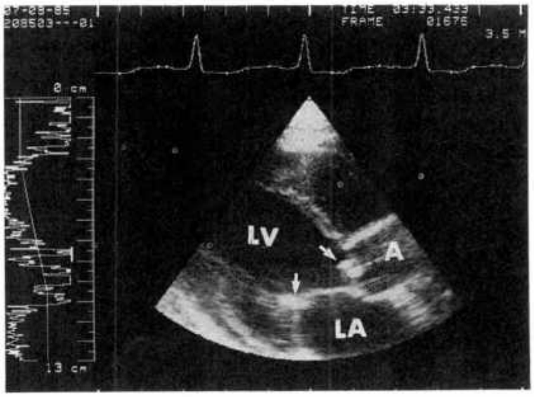

Fig 1 *Parasternal long axis cross sectional echocardiogram of patient 4 showing vegetations of the aortic and mitral valves (arrows).*

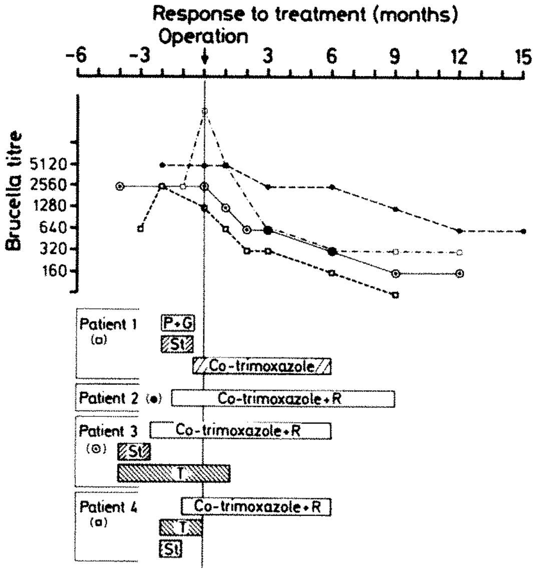

Fig 2 *Brucella titres and response to treatment. Co-trimoxazole (trimethoprim + sulphamethoxazole); St, streptomycin; T, tetracycline; R, rifampicin; P + G, penicillin and gentamicin.*

Six blood cultures were taken from each patient but only patient 3 had a blood culture that was positive for *Brucella melitensis* (the only biotype that was sought).

Cardiac catheterisation was performed in two patients (cases 1 and 4). In neither was an attempt made to cross the aortic valve for fear of embolism. Aortography showed severe aortic regurgitation in both and moderate mitral regurgitation in patient 4. The condition of patient 1 deteriorated further after angiography but he was stabilised and sent for operation the next day.

TREATMENT

Whatever the medical treatment the patients received before referral we elected to treat all patients in our institution with co-trimoxazole [Septra] (trimethoprim 10 mg/kg/day and sulphamethoxazole 20 mg/kg/day) and rifampicin 300–600 mg/day, except patient 1 who was given co-trimoxazole alone (fig 2). All patients required operation in the active stage. The indications for operation were acute left ventricular failure and pulmonary oedema secondary to severe aortic regurgitation in three patients, and fear of embolism in one patient with a previous embolic cerebrovascular accident and echocardiographic evidence of a pedunculated, freely mobile vegetation dangling into the left ventricular outflow tract.

At operation all patients had aortic valve vegetations. Three patients (cases 1, 2, and 4) had a cusp perforation. Two patients (2 and 4) had a detached leaflet. Patient 3 had an aortic root abscess. The patient in whom the mitral valve was affected had a vegetation with tear on the anterior leaflet of the mitral valve and ruptured chordae tendineae.

Histopathology showed inflammatory cell infiltration in all cases and Gram negative bacilli. *Brucella* was grown from samples taken from patients 1 and 2, but biotyping was not performed because *Br melitensis* is the most common cause of brucellous in Saudia Arabia.

All patients had aortic valve replacement and patient 4 also had mitral valve replacement. The aortic valves were replaced with the following prostheses: Smeloff-Cutler in patient 1, Saint Jude in 2 and 3, and Björk-Shiley in 4. The mitral valve was replaced with a Björk-Shiley prosthesis. There were no operative deaths. One patient (case 2) needed intra-aortic balloon support postoperatively and had a perioperative haemorrhagic cerebrovascular accident.

POSTOPERATIVE FOLLOW UP

In all patients *Brucella* titres, blood cultures, and echocardiography were repeated every three months for a year. Three months after operation all *Brucella* titres had dropped markedly except in patient 2 who had only one dilutional decrease. All showed further decreases at nine and twelve months (fig 2).

At follow up no patient had positive blood cultures or evidence of vegetations by echocardiography.

All patients continued their preoperative antibiotics (co-trimoxazole and rifamipicin) for six months after operation except patient 2 who had an additional three months' treatment because of a delayed drop in *Brucella* titre. During follow up (mean 15 months) there was no recurrence.

Discussion

Brucella endocarditis is the most common cause of death in human brucellosis. Peery and Belter found endocarditis in 80% and myocardial abscess in 43% of a series of 44 necropsies on cases of fatal brucellosis.[6] Dalrymple-Champneys observed only five cases of endocarditis among 1500 cases of human brucellosis in England over a period of 43 years[13]; Spink reported four cases in a series of 244 patients in the United States.[14] This low incidence of endocarditis in the West is not surprising as most of the cases were caused by *Br abortus*, a species known to cause mild disease with uncommon suppurative or disabling complications.[15 16] Endocarditis may be a more common complication of systemic brucellosis in countries where there is a high prevalence of *Br melitensis* and rheumatic heart disease since *Br melitensis* is known to cause more severe, acute disease associated with disabling complications.[15,17] In a review of endocarditis at King Faisal Specialist Hospital, *Brucella* endocarditis was seen in 8·5% of patients treated for endocarditis.[18]

As in previous reports of *Brucella* endocarditis, all our patients were men with a history of ingesting fresh, raw milk, and all had symptoms for at least three months before presentation.[7–12,19,20]

Review of published reports indicates that the aortic valve is affected in 75% of cases, and the mitral valve, mitral and aortic valves, and prosthetic valves are equally affected in 8·3% of cases. In three of our patients the aortic valve was affected and in the fourth both the aortic and mitral valves were affected.

Diagnosis of endocarditis in a course of brucellosis is difficult. A changing heart murmur, high *Brucella* titre, and echocardiography are helpful. A changing heart murmur with haemodynamic deterioration was seen in two of our patients while they were in hospital, and one patient was admitted with severe aortic regurgitation and pulmonary oedema. This also accords with other reports.[20]

The *Brucella* titre was very high (≥2560) in all our patients and it remained high or increased until operation. This relatively high *Brucella* titre in a course of *Brucella* endocarditis has been reported by Cohen *et al.*[20]

Echocardiography, by showing bulky vegetations in all four patients, was very helpful in establishing the diagnosis of endocarditis. In three patients premature closing of the mitral valve indicated aortic regurgitation.

Blood cultures were positive in only one patient. This low yield of blood cultures may be because of the fastidiousness of the organism, previous antibiotic treatment, and the long interval between onset of symptoms and diagnosis.[4]

Brucella endocarditis usually has an unremitting and fatal course with death occurring within three to eleven months of the onset of symptoms,[19] and usually from congestive heart failure. Cure with antimicrobial treatment alone[4,20–22] has been reported only in two doubtful cases with mixed bacterial endocarditis.[23,24] We elected to treat the patients in our institution with co-trimoxazole and rifampicin because rifampicin has been shown to be active against *Br melitensis*,[25,26] and co-trimoxazole is clinically effective against brucellosis.[27–31] All our patients needed operation in the active stage, however: three because of acute pulmonary oedema secondary to aortic valve destruction and the fourth because of fear of further embolic episodes. At operation all patients showed evidence of active disease.

Operation for *Brucella* endocarditis was reported in 1967 by Ehrenhaft, who replaced an infected aortic valve. The prosthetic valve became infected and the patient died after 38 days.[32] There are six reported cases of surgically cured *Brucella* endocarditis[7–12]: in five the aortic valve was affected and the sixth had an infected prosthetic (Starr-Edwards) mitral valve. All the five reported cases with aortic valve replacement had one to three months' antibiotic treatment after operation and the patient with an infected prosthetic mitral valve was treated for one year. Our patients had six months' treatment with co-trimoxazole and rifampicin after operation, and one had a further three months' treatment mainly because of delayed fall in *Brucella* titre (fig 2). There is no indication in published reports of how long antibiotic treatment should be continued after operation; however, six months seems to be adequate if the *Brucella* titre is falling. There was no evidence of recurrence of infection in any of our patients in more than 15 months' follow up.

References

1 Havas L. Problems and new developments in the treatment of acute and chronic brucellosis in man. *Acta Trop (Basel)* 1980;37:281–6.

2 Young EJ. Human brucellosis. *Rev Infect Dis* 1983;5:821–42.

3 Wise RI. Brucellosis in the United States, past, present and future. *JAMA* 1980;244:2318–22.

4 Salata RA, Ravdin JI. Brucellosis species (brucellosis). In: Mandell GL, Douglas RD, Bennett JE, eds. *Principles and practice of infectious diseases.* New York: John Wiley, 1985:1283–90.

5 Buchanan TM, Faber LC, Feldman RA. Brucellosis in the United States 1960–1972. An abattoir-associated disease. Part I. Clinical features and therapy. *Medicine (Baltimore)* 1974;53:403–13.

6 Peery TM, Belter LF. Brucellosis and heart disease. II Fatal brucellosis: a review of the literature and report of new cases. *Am J Pathol* 1960;36:673–97.

7 Wolf LM, Hazan E, Letac B, *et al.* Endocardite brucellienne. Guerison per remplacement valvulaire en periode evolutive. *Nouv Presse Med* 1973;2:493–5.

8 O'Meara JB, Eykyn S, Jenkins BS, *et al. Brucella melitensis* endocarditis: successful treatment of an infected prosthetic mitral valve. *Thorax* 1974;29:377–81.

9 Cleveland JC, Suchor RJ, Dague J. Destructive aortic valve endocarditis from *Brucella abortus*: survival with emergency aortic valve replacement. *Thorax* 1978;33:616–8.

10 Pratt DS, Tenney JH, Bjork CM, Reller LB. Successful treatment of *Brucella melitensis* endocarditis. *Am J Med* 1978;64:897–900.

11 Paxderka E, Jones JW. Brucella abortus endocarditis: successful treatment of an infected aortic valve. *Arch Intern Med* 1982;142:1567–8.

12 Heibig J, Beall A, Myers R, *et al.* Brucella aortic endocarditis corrected by prosthetic valve replacement. *Am Heart J* 1983;**106**:594–6.

13 Dalrymple-Champneys W. *Brucella infection and undulent fever in man.* London: Oxford University Press, 1960:1.

14 Spink WW. *The nature of brucellosis.* Minneapolis: University of Minnesota Press, 1956:145–90.

15 Spink WW. Some biologic and clinical problems related to intracellular parasitism in brucellosis. *N Engl J Med* 1952;**247**:603–10.

16 Spink WW. Host parasite relationship in brucellosis. *Lancet* 1964;**ii**:161–4.

17 Williams E. Brucellosis. *Practitioner* 1982;**226**:1507.

18 Halim M, Jeroudi M, Mercer E, *et al.* Infective endocarditis in King Faisal Specialist Hospital, review of 35 consecutive adult patients. *Annals of Saudi Medicine* 1986;**6**:179–83.

19 Hart FD, Morgan A, Lacey B. *Brucella abortus* endocarditis. *Br Med J* 1951;**i**:1048–53.

20 Cohen PS, Maguire JH, Weinstein L. Infective endocarditis caused by gram negative bacteria: a review of the literature 1945–1977. *Prog Cardiovasc Dis* 1980;**22**:205–42.

21 Buchanan TM, Petersdorf RG. Brucellosis. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's principles of internal medicine.* 10th ed. New York: McGraw-Hill, 1983:974–6.

22 Williams E. Brucellosis. In: Wetherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford textbook of medicine.* Oxford/London: Oxford University Press, 1983:5.221–6.

23 Quinn RW, Brown JW. Bacterial endocarditis. *Arch Intern Med* 1954;**94**:629–48.

24 Hudson RA. *Brucella abortus* endocarditis: a case. *Circulation* 1957;**16**:411–13.

25 Llorens-Terol J, Busquets RM. Brucellosis treated with rifampicin. *Arch Dis Child* 1980;**55**:486–8.

26 Binda G, Domenichini E, Gottardi A, *et al.* Rifampicin, a general review. *Arzneimittelforschung* 1971;**21**: 1907–77.

27 Dendikos GK, Papolyzos N, Marketos N, *et al.* Trimethoprim and sulfamethoxazole in brucellosis. *J Infect Dis* 1973;**128(S)**:S731–3.

28 Lal S, Modawal KK, Fowle AS, *et al.* Acute brucellosis treated with trimethoprim and sulphamethoxazole. *Br Med J* 1970;**iii**:256–7.

29 Hassan A, Erian MM, Farid Z, *et al* Trimethoprim-sulphamethoxazole in acute brucellosis. *Br Med J* 1971;**iii**:159–60.

30 Gunchi G, de Rose F, Fabini F. Treatment of brucellosis with trimethoprim-sulfamethoxazole. *Chemotherapy* 1971;**16**:332–5.

31 Lifeso RM, Harder E, McCorkell SJ. Spinal brucellosis. *J Bone Joint Surg [Br]* 1985;**67**:345–51

32 Ehrenhaft JL. In discussion of a paper by Kasier GC, Willman VL, Thurmann M, Hanlon CR. Valve replacement in cases of aortic insufficiency due to active endocarditis. *J Thorac Surg* 1967;**54**:491.

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Case reports

Diagnosis of double aortic arch by cross sectional echocardiography with Doppler colour flow mapping

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SUMMARY A case of double aortic arch in a 15 month old boy was diagnosed by cross sectional echocardiography supplemented by Doppler colour flow mapping. These examinations showed two very large vessels communicating with the aorta; the demonstration of anterograde flow in one vessel and retrograde flow in the other enabled a definite diagnosis of Edwards type IA double aortic arch to be made.

Early surgical intervention is often required in infants and children with double aortic arch who show symptoms caused by tracheal or oesophageal compression.[1] Definite diagnosis is made by aortography, which is an invasive procedure. Real time cross sectional echocardiography is a useful non-invasive method of detecting this anomaly,[2 3] but the diagnosis depends on several factors such as ease of obtaining a suprasternal examination and identification of the oesophagus, both of which may be difficult in a small child. Also it may be difficult to discriminate between a bifurcated aortic arch and a dilated cephalic branch or aberrant vessel arising from a non-bifurcated aortic arch. The diagnosis often relies on exact positioning or orientation of the transducer. Both are subjective and liable to error. We present a case in which a double aortic arch was diagnosed by cross sectional echocardiography supplemented by Doppler colour flow mapping. We used a high parasternal approach rather than the previously used subcostal or suprasternal approach.

Case report

A 15 month old boy presented with moderate respiratory distress and a history of recurrent upper respiratory tract infections. Coarse rhonchi were heard throughout the lung fields. A cross sectional echocardiogram performed through a high parasternal window showed a large vessel, about the same size as the aortic arch, arising from the ascending aorta. A second vessel, about the same size as the first vessel, was seen joining the upper portion of the descending aorta in the same plane. Colour flow mapping (Aloka 880 system) showed blood flowing from the ascending aorta into the first vessel and moving in an opposite direction from the second vessel into the descending aorta (fig 1).

Discussion

The cross sectional echocardiographic findings were of two very large vessels communicating with the aorta. Colour Doppler showed blood flowing anterogradely in the first vessel and retrogradely in the second vessel and enabled us to make a definite diagnosis of Edwards type IA double aortic arch.[4] Colour Doppler flow mapping supplemented cross sectional echocardiography and assisted diagnosis. Angiography confirmed the cross sectional echocardiographic findings (fig 2). Surgical resection was successful and the child showed considerable clinical improvement.

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References

1 Gross RE. Arterial malformations which cause compression of the trachea or esophagus. *Circulation* 1955;11:124–34.

2 Sahn DJ, Valdes-Cruz IM, Quit TW, *et al.* Two-dimensional echocardiography and intravenous digital video subtraction angiography for diagnosis and

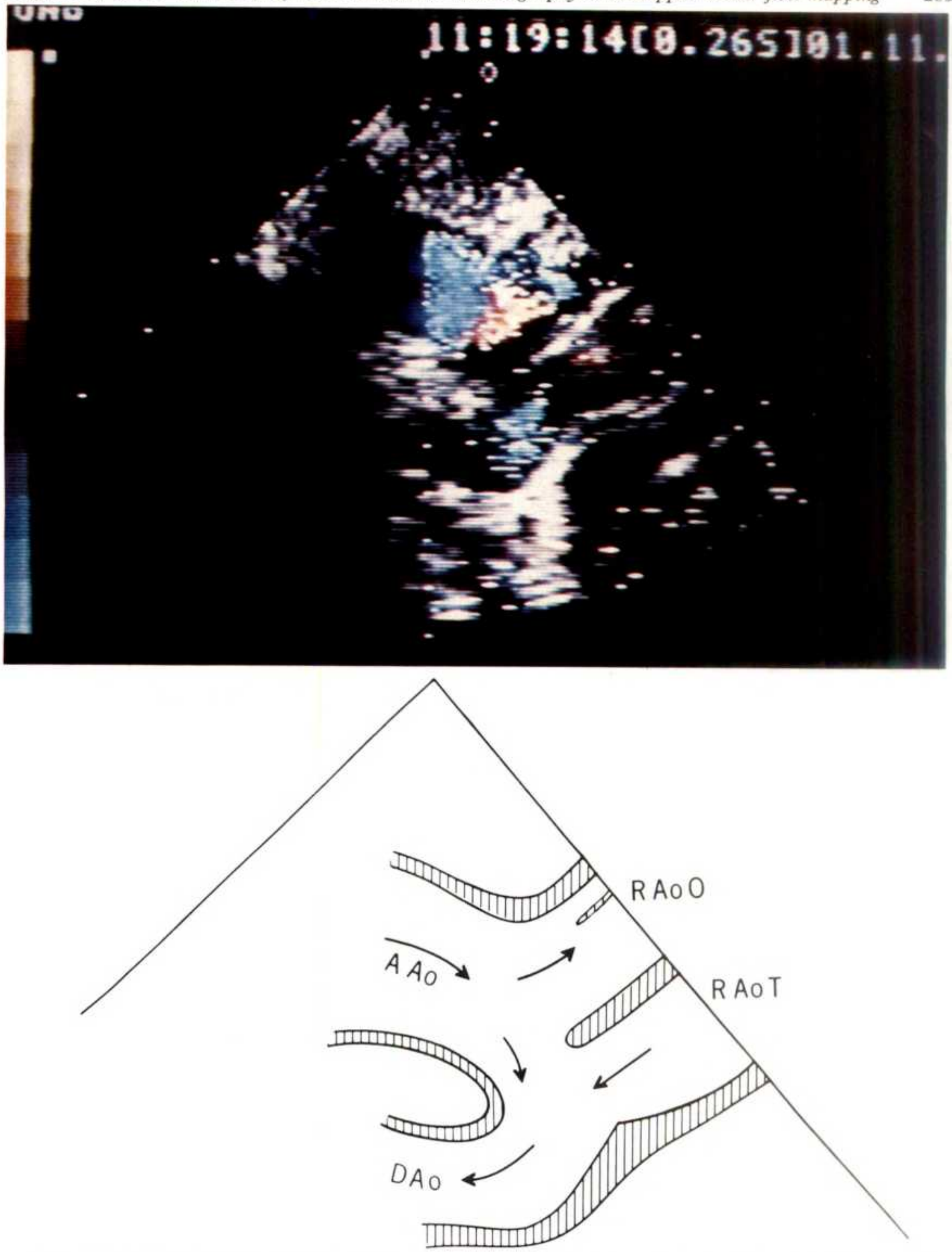

Fig 1 *Cross sectional and Doppler colour flow mapping from the high parasternal approach in a case of double aortic arch. Two very large vessels communicated with the aorta. Colour flow study showed blood flowing into the first vessel (RAoO) from the ascending aorta (AAo) and retrogradely from the second vessel (RAoT) into the descending aorta (DAo). Red indicates flow toward the transducer and blue shows flow away from transducer. RAoO, origin of the right aortic arch; RAoT, termination of the right aortic arch.*

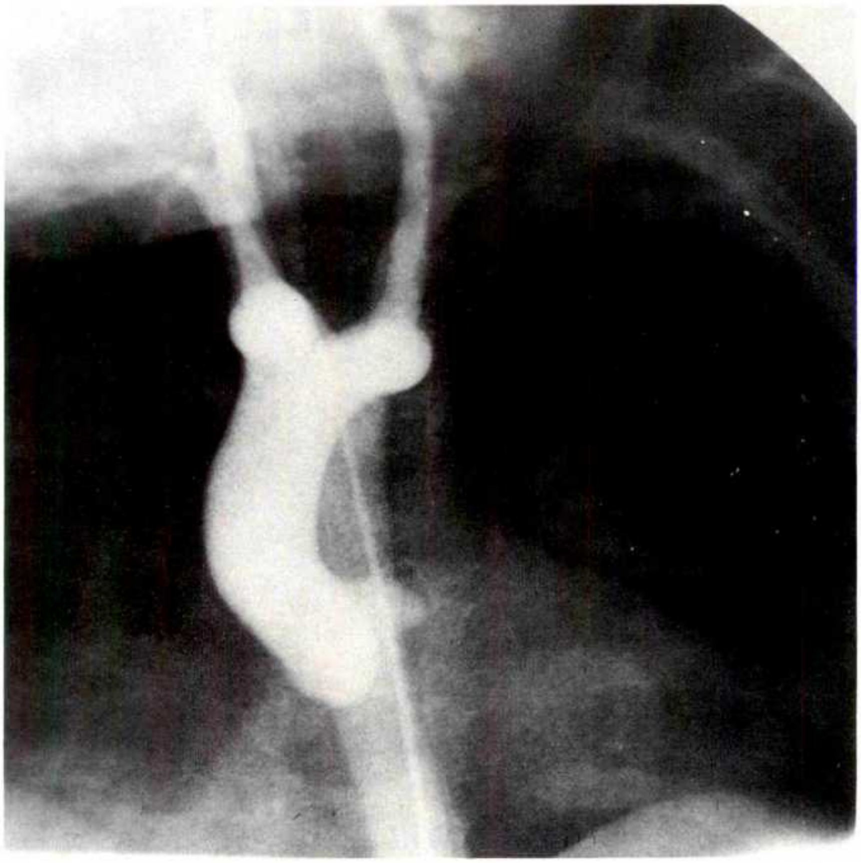

Fig 2 *Aortography showing double aortic arch.*

evaluation of double aortic arch. *Am J Cardiol* 1982;**50**:342–6.

3 Enderlein MA, Silverman NH, Stanger P, Heymann MA. Usefulness of suprasternal notch echocardiography for diagnosis of double aortic arch. *Am J Cardiol* 1986;**57**:359–61.

4 Stewart JR, Kincaid OW, Edwards JE. *An atlas of vascular rings and related malformations of the aortic arch system.* Springfield, Illinois: Charles C Thomas, 1964.

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Infection of modified Blalock shunts

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SUMMARY A left-sided interposition graft (modified Blalock-Taussig anastomosis) was constructed with polytetrafluoroethylene in a three month old child with tetralogy of Fallot. This shunt thrombosed and a replacement shunt became the site of chronic *Pseudomonas* infection. The second anastomosis was excised and a third interposition graft was inserted on the right side because the anatomy was unsuitable for a classical Blalock-Taussig shunt. The patient died when he was 12 months old, after signs of infection and shunt occlusion had developed. At necropsy the acutely thrombosed right sided shunt was found to be the site of *Candida albicans* infection. Gallium and labelled white cell scans, computed tomography, and ultrasound scans had all failed to identify the sites of infection, which were only confirmed at operation or necropsy.

Subclavian to pulmonary artery shunts constructed from interposed grafts of polytetrafluoroethylene have been widely used since the introduction of this material to vascular surgery.[1] Such shunts are easy to construct and take down, they are less likely to distort the pulmonary arteries, they preserve flow to the subclavian artery (avoiding ischaemia of the arms), and they can provide adequate blood flow to both lungs.[2 3] Early thrombosis, particularly in neonates, is less common after this shunt procedure than after a classic Blalock-Taussig shunt.[3] Complications reported after the modified Blalock shunt include excessive pulmonary blood flow,[4] seroma formation,[5] and false aneurysm.[6]

We describe an infant, who probably had an immunological disorder, in whom successive shunts became infected with different organisms. These infections eventually led to his death.

Case report

A left-sided modified Blalock shunt (5 mm Impra graft) was constructed soon after the onset of hypercyanotic spells in a three month old boy with tetralogy of Fallot. His colour did not improve and a shunt murmur was not audible. In addition, there was a hypercyanotic spell on the first postoperative day. Angiography showed poor filling of the shunt because of a proximal stenosis. At reoperation the shunt was replaced by a second 5 mm Impra graft. His colour and arterial Po_2 improved considerably and a loud continuous murmur was audible. Artificial ventilation was required for four days because he had left phrenic nerve palsy. Two and six weeks after operation there were episodes of acute infection and blood cultures were positive for *Pseudomonas aeruginosa*. An intensive search for a focus of infection with ultrasound, computed tomography, and white cell scan incriminated only the left lower lobe of the lung. A sweat test for cystic fibrosis was negative. After a prolonged antibiotic course with azlocillin, amikacin, and benzylpenicillin he recovered and was transferred to another hospital for management of feeding difficulties. While he was there he had several episodes of *Pseudomonas aeruginosa* septicaemia and left-sided pneumonia despite appropriate antibiotic treatment.

At the age of nine months he weighed 5·6 kg and was mildly cyanosed with clubbed fingers; the liver was palpable 3 cm below the right costal margin. The respiratory rate was 40 per minute with subcostal recession and bilateral crepitations. The shunt murmur was easily audible. Infection of the Impra graft was strongly suspected. A right thoracotomy was performed with the intention of constructing a right classic Blalock-Taussig shunt before excision of the left shunt. The anatomy was unfavourable, however, and a 5 mm Impra graft was inserted on the right. A left thoracotomy was performed. Dense adhesions were found. The subclavian artery was

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ligated and divided, the left Impra graft was completely excised, and the left pulmonary artery was repaired with a patch of autologous pericardium. After operation he was treated with intravenous azlocillin and amikacin for 21 and 14 days respectively. *Pseudomonas aeruginosa* sensitive to these antibiotics was isolated from this shunt. Six days after operation, while he was still on the ventilator, he became acutely unwell and *Candida* was cultured from the tip of an indwelling urinary catheter. He was treated with flucytosine and he improved gradually with no further evidence of *Candida* infection. When antibiotic treatment was stopped, however, episodes of fever and leucocytosis occurred. Screening for sepsis was negative on all these occasions. A chest radiograph showed bilateral chronic patchy opacities and there was a widening of the mediastinum on the right. Tests of immunological function were generally abnormal, with reduced complement components, reduced *Saccharomyces* opsonins and a serum-dependent neutrophil killing defect for *Candida albicans*. Concentrations of IgG, IgA, IgM, and IgE were all raised, as was the C-reactive protein (20 mg/l), which indicates active infection at the time of the study. The patient did not react to *Candida* skin tests. Finally, repeated blood cultures grew *Straphylococcus epidermidis*. A gallium scan showed no evidence of focal infection. He was treated with flucloxacillin, fucidic acid, and several infusions of fresh frozen plasma, and his general condition and the appearance of the chest radiograph improved dramatically. The right mediastinal shadow persisted and was thought to represent organised haematoma around the right shunt. In the mean time, plication of the left hemidiaphragm was performed because of continued ventilator dependence. He was eventually extubated three weeks after this procedure. He was again transferred to another hospital for convalescence.

Two weeks later he became acutely ill and cyanosed. The shunt murmur was inaudible. He had a fever and signs of disseminated intravascular coagulation, and despite treatment with antibiotics and pressor agents he died. At necropsy no pus was found either near the shunt or elsewhere. There was no sign of endocarditis. The right Impra graft contained recent thrombus that occluded the lumen. The shunt was surrounded by a greenish-brown mass 1·8 cm in diameter which compressed but did not invade the right upper lobe (fig 1). Microscopy of this mass showed organising Surgicel and fibrin traversed by scores of *Candida* hyphae. Microscopy of the thrombus showed collections of neutrophils and the presence of *Candida* yeasts and pseudohyphae (fig 2). Large numbers of alveolar macrophages with a light lymphocytic infiltrate were seen

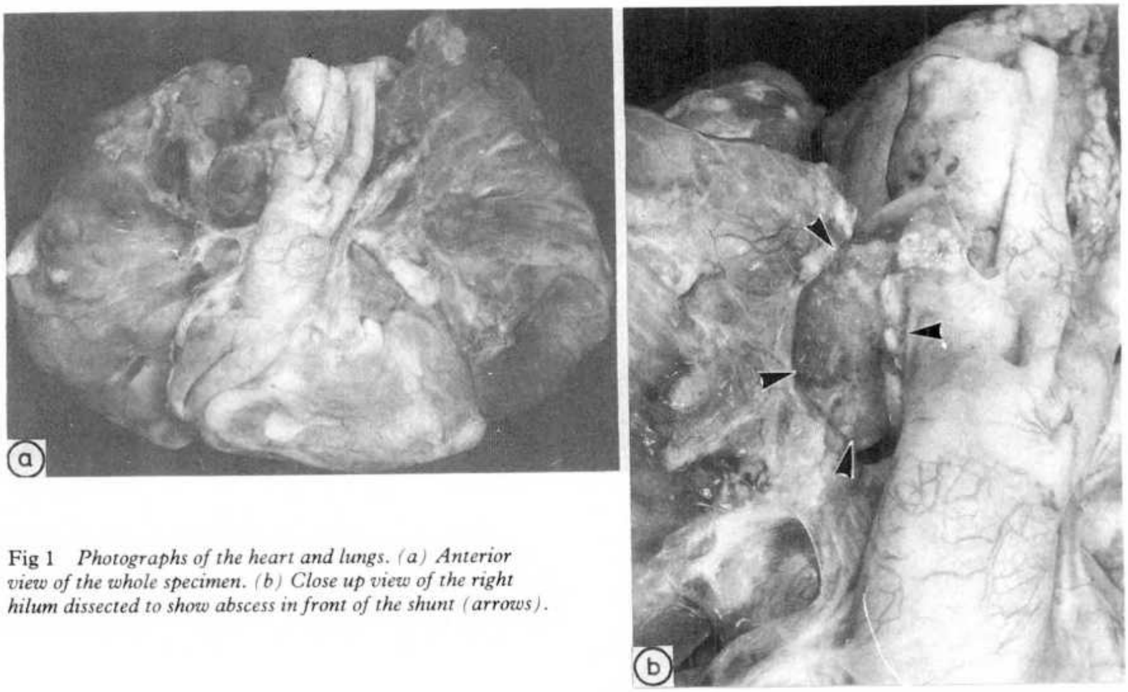

Fig 1 *Photographs of the heart and lungs. (a) Anterior view of the whole specimen. (b) Close up view of the right hilum dissected to show abscess in front of the shunt (arrows).*

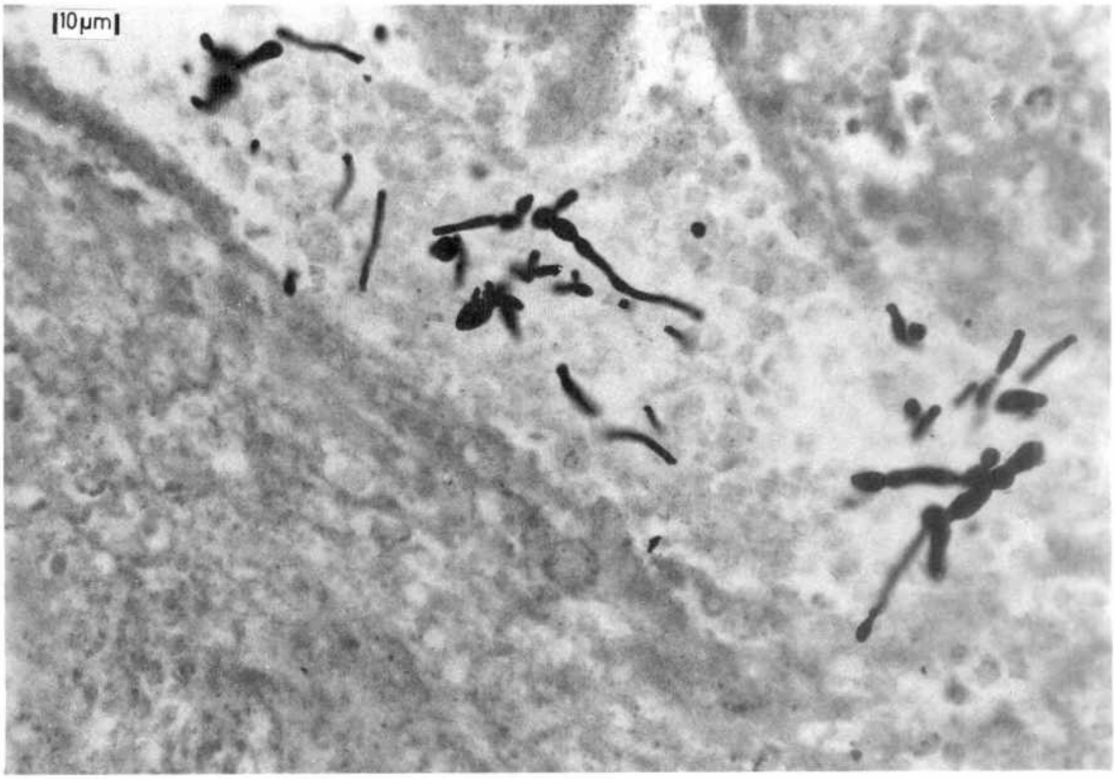

Fig 2 *Photomicrograph of the thrombus showing numerous Candida pseudohyphae growing within organising fibrin.*

in lung sections. There was no evidence of bronchopneumonia and in the lungs stains for *Candida* and other micro-organisms were negative.

Discussion

The modified graft constructed from polytetrafluoroethylene effectively palliates children with congenital heart disease who have reduced pulmonary blood flow and, although it offers advantages over the classic Blalock-Taussig anastomosis, complications occasionally occur. Formation of false aneurysms in patients with polytetrafluoroethylene grafts was reported and ascribed to infection. Monarrez *et al* attempted to excise a shunt that was presumed to be infected and in which detachment of the proximal end had resulted in pseudoaneurysm formation.[6] The patient died of uncontrollable blood loss. The shunt was occluded by a sterile thrombus. No mention was made of the results of bacterial culture of the graft. Opie *et al* described five patients with polytetrafluoroethylene grafts in whom ipsilateral pneumonia developed within six months of operation.[4] In two patients with positive blood cultures, aneurysms developed that were associated with the shunt. In neither case, however, were results of bacterial culture of the shunt given.

Confirmation of an infection affecting a prosthetic shunt may be difficult. In the present case none of the investigations designed to find the site of chronic infection pointed to either of the last two shunts. Eventually only surgery to resect the shunt and subsequent direct bacteriological culture proved that the left Impra graft was indeed infected. Proof of sepsis in the right Impra graft was only obtained at necropsy. In view of this experience, we agree with others[4 6] that the occurrence of repeated episodes of septicaemia, late shunt thrombosis, and the development of aneurysms related to the shunt are all strong indicators of graft sepsis. Definitive treatment should not be delayed because diagnostic investigations are negative. Mediastinal enlargement on the chest radiograph is more likely to be caused by haematoma or seroma[5] than pseudoaneurysm secondary to shunt infection. In the presence of other suspicious features, however, angiography should be performed to identify the cause.[6]

We do not know whether the repeated infections and graft sepsis were a result of a primary immune deficiency affecting neutrophil and complement dependent mechanisms, or whether the abnormal results of immunological function were secondary to chronic infection caused by deep-seated graft sepsis (with continual seeding of the blood stream) and recurrent pneumonia. We were not able to perform immunological tests when he was clinically well.

The management of shunt infection may be difficult. When a pseudoaneurysm is present there will be torrential bleeding at the time of excision.[6] Because prosthetic material used either to create another shunt or to correct the intracardiac anomaly may be contaminated the use of the classic Blalock-Taussig or even Waterston shunt may be preferred. Bovine pericardium sterilised with antibiotic may be better than synthetic cloth for the closure of ventricular or atrial septal defects or both. A complete course of the appropriate intravenous antibiotics should be given when any infection is diagnosed soon after construction of a prosthetic shunt. If the same organism is repeatedly isolated after the end of antibiotic treatment, a shunt infection must be presumed to exist and the septic graft should be removed without delay. It can be disastrous to wait for the results of expensive and complicated tests whose sensitivity and specificity for diagnosing shunt infection are unknown.

We thank Dr A J Pinching, Department of Immunology, St Mary's Hospital Medical School, for performing the tests of immunological function; Dr E A Sheffield, Department of Histopathology, Brompton Hospital; Dr M L Rigby for permission to report this case; and Dr E A Shinebourne for his helpful advice. J S C is supported by CNPq-Brazilian Research Council.

References

1 Gazzaniga AB, Lamberti JJ, Siewers RD, *et al.* Arterial prosthesis of microporous expanded polytetrafluoroethylene for construction of aorta-pulmonary shunts. *J Thorac Cardiovasc Surg* 1976;72:357–63.

2 Lamberti JJ, Carlisle J, Waldman JD, *et al.* Systemic-pulmonary shunts in infants and children. *J Thorac Cardiovasc Surg* 1984;88:76–81.

3 Ilbawi MN, Grieco J, DeLeon S, *et al.* Modified Blalock-Taussig shunt in newborn infants. *J Thorac Cardiovasc Surg* 1984;88:770–5.

4 Opie JC, Traverse L, Hayden RI, Ho CY, Culham JAG, Ashmore PG. Experience with polytetrafluoroethylene grafts in children with cyanotic congenital heart disease. *Ann Thorac Surg* 1986; 41:164–8.

5 LeBlanc J, Albus R, Williams WG, *et al.* Serous fluid leakage: a complication following the modified Blalock-Taussig shunt. *J Thorac Cardiovasc Surg* 1984;88:259–62.

6 Monarrez CN, Montalvo RF, Conti VR, Sapire DW. Septic involvement of polytetrafluoroethylene (PTFE) anastomosis producing false aneurysm: diagnosis and problems related to management. *Pediatr Cardiol* 1984;5:297–300.

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Treatment of glossopharyngeal neuralgia by carbamazepine

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SUMMARY An elderly woman who presented with Adams-Stokes attacks that were preceded by paroxysms of neuralgia was successfully treated with carbamazepine. Ventricular asystole was provoked by pharyngeal pain and coincided with loss of consciousness. Vagal reflexes are probably responsible for the bradycardia that causes the cardiac symptoms of glossopharyngeal neuralgia. Carbamazepine (600 mg/day) abolished the pharyngeal pain and associated cardiovascular manifestations in this patient for at least ten months.

Glossopharyngeal neuralgia is a rare cause of syncope. Neuralgia in the throat and neck triggers severe bradycardia up to asystole, and this leads to cardiac syncope, sometimes with seizures.[1 2] We report the case of an elderly woman who had syncopal attacks preceded by paroxysms of neuralgia. This patient was successfully treated with carbamazepine (Tegretol).

Case report

An 83 year old woman was admitted in October 1985 because of Adams-Stokes attacks, which were preceded by excruciating pain in the left ear and pharynx. Pain was provoked by swallowing and head movements. She had had typhoid fever as an infant and glomerulonephritis as a young adult. She reported episodes of chest pain over the past ten years that subsided with sublingual glyceryl trinitrate; these were managed as sporadic angina. She was admitted to the coronary care unit where an abrupt slowing down of the heart rate to 20–25 beats/minute with concomitant loss of consciousness and convulsive movements were noted during continuous electrocardiographic monitoring. A temporary transvenous pacemaker was inserted to prevent prolonged asystole and syncope. A few hours later a sharp pain in the left ear and throat was precipitated by coughing. This was followed by asystole, which was interrupted by pacemaker intervention. She had a 3/6 systolic ejection murmur that was loudest at the fourth left parasternal intercostal space and radiated to the neck. This murmur was compatible with mild aortic stenosis. There were no abnormal neurological signs. Blood chemistry was within normal limits, except for a haemoglobin concentration of 10 mg/dl and slightly increased blood glucose and urea nitrogen.

Chest *x* ray showed cardiomegaly, aortic calcification, and pulmonary emphysema. Electroencephalography and computed tomography of the brain were normal. The electrocardiogram showed sinus bradycardia (42 beats/minute), anterior hemiblock, and inverted T waves in III and a VF. Echocardiographic findings were compatible with calcific aortic stenosis of moderate degree and good left ventricular systolic function. The results of endoscopy of the upper gastrointestinal tract were normal.

The clinical picture led to a diagnosis of cardiac syncope due to glossopharyngeal neuralgia. To confirm the diagnosis, the patient was asked to drink carbonated water. This provoked pharyngeal pain and, almost immediately, ventricular asystole (5·0 s), accompanied by feeling lightheaded. Carotid sinus massage did not produce pain or severe bradycardia. On the other hand, after the pacemaker was switched off, intravenous atropine sulphate (2·0 mg) prevented ventricular asystole despite continuing pharyngeal pain.

Because she had a history of chest pain, sympathomimetic agents, such as isoprenaline, were not tried. When the patient was started on carbamazepine (Tegretol) 600 mg/day there was a prompt symptomatic improvement. There were no major side effects. The temporary pacemaker was then removed because it was regarded as unneces-

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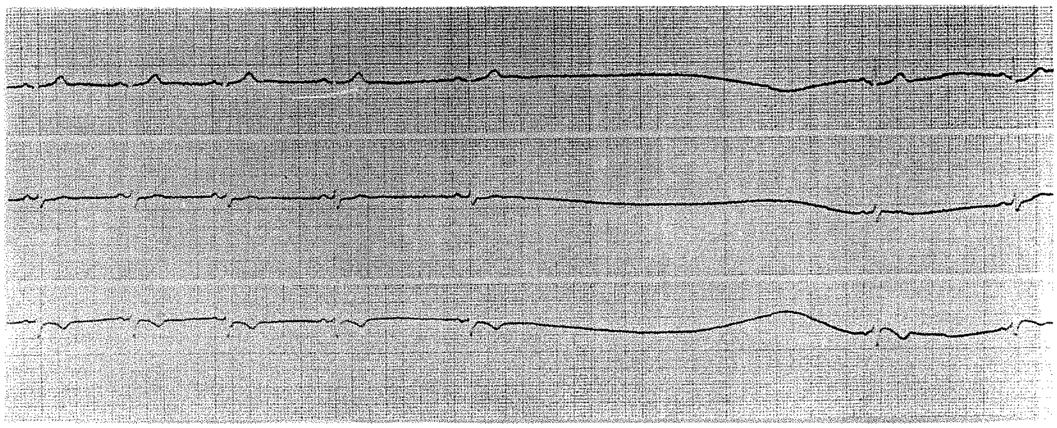

Figure *Electrocardiogram (leads I, II, III (from top to bottom); paper speed 25 mm/s) showing sinus arrest lasting 4·8 s after pharyngeal pain evoked by drinking carbonated water.*

sary in the absence of recurrent syncope. Ten months after treatment was started the patient remains symptom free on carbamazepine.

Discussion

Glossopharyngeal neuralgia was first described by Weisenburg in 1910 in a patient with a tumour of the cerebello-pontine angle.[3] Riley *et al* in 1942 were the first to report a cardiac arrest associated with neuralgia.[4] The cause of this disorder was usually undetermined, though in a few reported cases cerebello-pontine angle tumours[1] or an elongated styloid process or a calcified stylohyoid ligament or both[5] were identified as aetiological factors. These may cause chronic compression of nerves during swallowing. Some cases improved with surgical resection of the anomalous process.[5]

It is likely that vagal reflexes, initiated by glossopharyngeal neuralgia, are involved in the arrhythmias most commonly found in this syndrome, that is, sinus arrest, sinus bradycardia, and wandering atrial pacemaker.[6] Hypersensitivity of the carotid sinus is not a factor in glossopharyngeal neuralgia because massage of the sinuses does not reproduce the typical cardiovascular signs.[1 2] The paroxysms of pain are triggered by swallowing, particularly cold, salted, bitter, or acid foods[2 6] and by mechanical stimulation of the tonsillar fossa on the affected side (trigger zone).

Treatment aims at abolishing dysphagia and the ensuing bradycardia-syncope reflex. Atropine and isoprenaline, together with a temporary pacemaker, are used as emergency measures, but are not suitable for long term treatment because they do not relieve the neuralgia. Local anaesthesia of the pharynx and nerve block with mepivacaine (carbocaine) are additional measures that produce temporary benefit.[2 6] Anticonvulsant treatment (phenytoin) was advocated as the long term treatment of choice.[7] However, the clinical response of glossopharyngeal neuralgia to phenytoin was variable.[6-8] Carbamazepine is an effective treatment of trigeminal neuralgia, and may also be an alternative to phenytoin in the medical management of glossopharyngeal neuralgia. In our case carbamazepine was effective at relatively low dosage (600 mg/day or 10 mg/kg/day) in abolishing paroxysms of pain and associated cardiovascular manifestations for at least ten months without any side effects. Our findings indicate that carbamazepine may be an alternative to surgical resection of the glossopharyngeal nerve, which remains the most effective cure.

References

1 Garretson HD, Elvidge AR. Glossopharyngeal neuralgia with asystole and seizures. *Arch Neurol* 1963;**8**:26–31.
2 Kong Y, Heyman A, Entman ML, *et al*. Glossopharyngeal neuralgia associated with bradycardia, syncope and seizures. *Circulation* 1964;**30**:109–13.
3 Weisenburg TH. Cerebello-pontine tumor diagnosed for six years as tic douleureux; the symptoms of irritation of the ninth and twelfth cranial nerves. *JAMA* 1910;**54**:1600–4.
4 Riley HA, German WJ, Wortis H, *et al*. Glossopharyngeal neuralgia initiating or associated with cardiac arrest. *Trans Am Neurol Assoc* 1942;**68**:28–9.
5 Graf CJ. Glossopharyngeal neuralgia and ossification of the stylohyoid ligament. *J Neurosurg* 1959;**16**:448–53.
6 Khero BA, Mullins CB. Cardiac syncope due to glossopharyngeal neuralgia. *Arch Intern Med* 1971;**128**:806–8.
7 Jannone A, Baker AB, Morrell F. Dilantin in the treatment of trigeminal neuralgia. *Neurology* 1958;**8**:126–8.
8 Kersley JA. A case of glossopharyngeal neuralgia. *J Laryngol Otol* 1965;**79**:734–7.

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Aortic valve endocarditis associated with *Legionella* infection after *Mycoplasma* pneumonia

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SUMMARY A 38 year old woman with diabetes mellitus and bronchial asthma was admitted to hospital with pneumonia caused by *Mycoplasma pneumoniae*; she recovered promptly on erythromycin treatment. Six weeks later she presented with aortic valve endocarditis without concurrent lung disease. A concurrent increase in titres of antibody to *Legionella bozemanii*, *L longbeachae*, and *L jordanis* indicated a *Legionella* infection.

Legionella infection should be considered, even in the absence of pneumonia, in cases of endocarditis where no other cause can be detected.

Although *Legionella* is known to cause pericarditis and myocarditis,[1] only one case of endocarditis associated with *Legionella* infection has been reported.[2] This patient had undergone mitral and aortic valve replacement with porcine xenografts one month before the infection.

We describe a woman with aortic valve endocarditis who had a concurrent rise in titres of antibodies to *Legionella* a month after pneumonia caused by *Mycoplasma pneumoniae*.

Case report

A 38 year old white woman was admitted on 19 October 1984 after a six day history of fever (up to 40°C), productive cough, right-sided pleuritic chest pain, and dyspnoea on exertion. She had insulin dependent diabetes mellitus and bronchial asthma, but no history of heart disease.

Pneumonia caused by *M pneumoniae* was diagnosed on the basis of her symptoms, clinical findings, a chest *x* ray showing infiltration of the right lower and middle lobes, and a significant rise in the titre of complement fixing antibodies to *M pneumoniae* and a high titre of cold agglutinins[3] (figure). The heart sounds were normal. Investigations showed: erythrocyte sedimentation rate 120 mm/h, leucocyte count 10·8 × 10^9/l (71% neutrophils, 23% lymphocytes), blood pressure 130/80 mm Hg. Blood, throat, and sputum cultures yielded no pathogens. Serological tests for ornithosis were non-diagnostic. The patient was given erythromycin 500 mg three times a day for two weeks and there was a prompt clinical recovery. A chest *x* ray after discharge (23 November 1984) was normal.

The patient returned to the clinic on 19 December 1984 complaining of general malaise and fever (up to 39°C) at night. On physical examination she was afebrile with a heart rate of 76 beats/min and a blood pressure of 170/90 mm Hg. A low frequency, pansystolic, crescendo murmur (grade 3/6) with radiation to the left axilla was heard on auscultation. No diastolic murmur was heard. There was no oedema or cyanosis. Auscultation of the lungs and the rest of the physical examination showed nothing abnormal. On admission investigations showed: haemoglobin 10·6 mmol/l, leucocytes 6·2 × 10^9/l (40% neutrophils, 54% lymphocytes). Chest *x* ray and electrocardiogram were within normal limits. An echocardiogram three days after admission showed a thickened bicuspid aortic valve with a 5–7 mm vegetation and a 3 mm pericardial effusion.

The titre of *M pneumoniae* antibodies was still high (2000) although the cold agglutinin titre had fallen to 8 (figure). Initial blood cultures for pathogenic bacteria were negative on six occasions and so were cultures from urine, throat, and sputum samples. Cultures from throat (1 January) and blood (18 January) were negative for *M pneumoniae*. Tests for antibodies to *Coxiella burnetii*, *Chlamydia psittaci*, and *Brucella abortus* were negative. We tested serum samples for antibodies to *Legionella*, including sera

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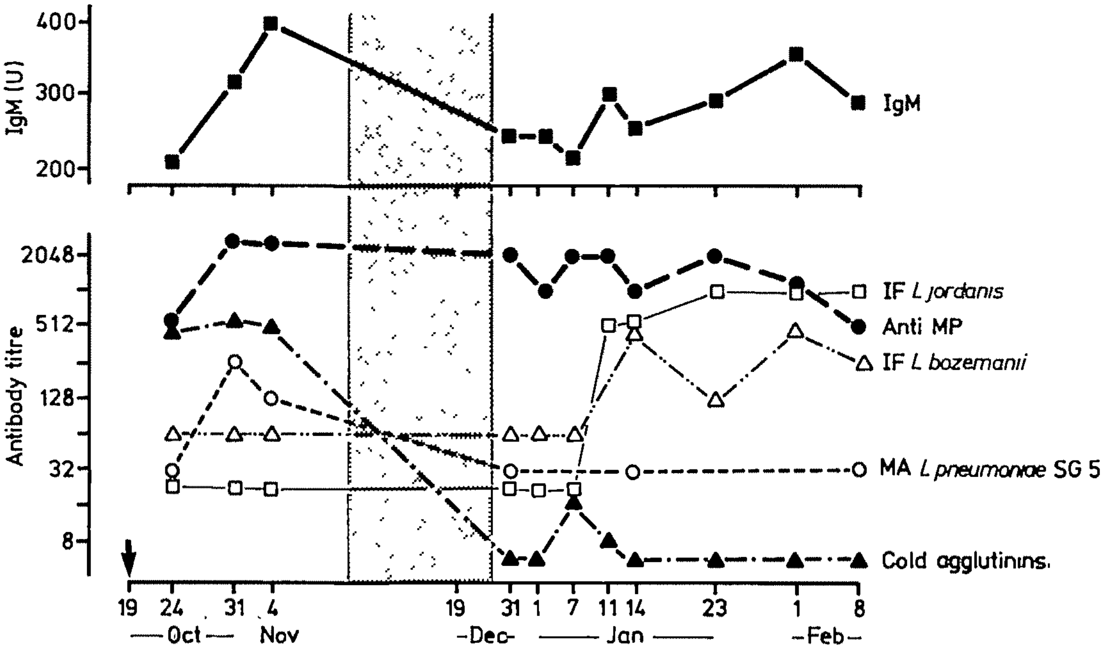

Figure *The patient was admitted with pneumonia on 19 October (black arrow) and readmitted with endocarditis on 19 December (white arrow). The diagram shows antibody titres by indirect immunofluorescence (IF) to Legionella jordanis and to Legionella bozemanii; by microagglutinin (MA) to Legionella pneumophila serogroup 5; to anti-Mycoplasma pneumoniae (MP) by complement fixation. Cold agglutinin titres and total serum IgM (normal range 80–322 units) are also shown. The stippled area indicates a period without blood sampling.*

from the first admission in October, by the indirect immunofluorescence test and all were negative for the following antigens: *L pneumophila*, serogroups (SG) 1–6, *L micdadei*, *L bozemanii*, *L dumoffii*, *L gormanii*, *L longbeachae*, SG 1 and 2, and *L jordanis*.[4]

The patient continued to have fever (38·5°C–39·0°C) at night. Twelve further blood specimens were drawn at 11 and 12 pm and 1 am on four consecutive nights; they remained negative on culture. A repeat echocardiogram on 2 January 1985 showed no change in the aortic valve vegetations, but mild, apparently haemodynamically insignificant aortic regurgitation was noted. Empiric antibiotic treatment with intraveneous penicillin 5 M IU four times a day and netilmicin 100 mg three times a day was started on 3 January. Nightly fever spikes continued, and titres of antibodies to *L bozemanii* and *L longbeachae* SG 1 and 2 rose significantly to 512 while antibody titres to *L jordanis* rose to 1024 in the indirect immunofluorescence test in which "blocking fluid" extracted from *Escherichia coli* was used as a serum diluent[5] (figure). *Mycoplasma* antibody titres remained at 1000–2000. Antibiotic treatment was switched to intravenous erythromycin 1 g four times a day from 18 January, and after three days the nightly fever spikes abated.

Chest *x* ray was still normal and an echocardiogram on 18 February was unchanged. After 6 weeks' treatment, intravenous erythromycin was changed to 1 g orally three times a day; this treatment was given for two weeks.

Discussion

This patient presented with two episodes of infectious disease. The first was severe acute pneumonia which was believed to be caused by *M pneumoniae* because there was a rise in specific antibody titre and a high transitory cold agglutinin titre. Attempts to isolate the organism two months after the acute illness were unsuccessful. One month after presenting with pneumonia the patient had an aortic valve endocarditis confirmed by clinical findings and echocardiography. The endocarditis was accompanied by a considerable rise in titre of antibodies to *Legionella*, indicating a causal assocation; however, we did not attempt to isolate the organism and there were no signs of pulmonary infection.

We considered the possibility that during the first episode *M pneumoniae* might have evoked an anamnestic response of antibodies to *Legionella* because *M pneumoniae* is a known to be a polyclonal B-cell activator.[6] Therefore, concentrations of total serum IgM and IgG were measured retrospectively in all serum specimens.[7] The results (figure) indicate that the typical increase in serum IgM during the *M pneumoniae* infection had abated before the endocarditis occurred and before the start of the rise in *Legionella* antibody titre detected by the indirect immunofluorescence test. During the first three weeks of this episode there was a second but less steep increase in serum IgM that was accompanied by a slight drop in *M pneumoniae* antibody titre. Changes in IgG concentration followed the IgM changes but were less pronounced (not shown). We also tested all serum specimens for *Legionella* antibodies in a microagglutination test.[8] We found a significant rise in titre of antibodies to *L pneumophila* SG 1 (to 64, not shown) and SG 5 (to 256, figure) during the first episode that paralleled the rise in total IgM. Antibodies to the other 11 *Legionella* antigens mentioned above remained at the same titre until the episode of endocarditis, when titres of antibodies to *L bozemanii* and *L longbeachae* SG 1 and 2 also rose in the microagglutination test (not shown in figure).

We believe that the first rise in antibodies to *L pneumophila* serogroup 1 and 5 was an anamnestic response and that the later increase in titre of both immunofluorescent and microagglutination antibodies to *L bozemanii* and *L longbeachae* indicates that the endocarditis may have been caused by a *Legionella* infection. The patient had insulin dependent diabetes and a chronic bronchial asthma; both increase the risk of *Legionella* infection. This risk was probably further increased by the previous *M pneumoniae* infection, which is known to depress cellular immunity.[9]

In the other report on a case of endocarditis caused by *L pneumophila,* the heart was infected in the absence of pneumonia[2]; this was the case in our patient too. The species or serogroup of *Legionella* which may have caused the infection in our patient cannot be deduced from antibody determination because of interspecies, often unpredictable, antigenic cross-reactions.[5] When antibody titres to other pathogens increase during an infection with *M pneumoniae* serodiagnosis is difficult because this organism is known to cause anamnestic antibody responses.[3] Several studies have found that antigens of *M pneumoniae* do not cross react serologically with *Legionella* antigens.[5]

We conclude that the possibility of *Legionella* infection should be considered in cases of endocarditis where no other cause can be shown, and that the absence of pneumonia does not exclude the possibility of a *Legionella* infection.

We thank Bendt Mansa, Deparment of Biophysics, Statens Seruminstitut, for measuring serum IgM and IgG.

References

1 Woodhead MA, MacFarlane JT. The protean manifestations of Legionnaires' Disease. *J R Coll Physicians Lond* 1985;**19**:224–30.

2 McCabe RE, Baldwin JC, McGregor CA, Miller DC, Vosti KL. Prosthetic valve endocarditis caused by *Legionella pneumophila. Ann Intern Med* 1984; **100**:525–7.

3 Lind K, Bentzon MW. Epidemics of *Mycoplasma pneumoniae* infection in Denmark from 1958 to 1974. *Int J Epidemiol* 1976;**5**:267–77.

4 Lind K. Serological investigations of *Legionella* infections in Denmark. *Acta Pathol Microbiol Immunol Scand [B]* 1983;**91**:209–13.

5 Wilkinson HW, Reingold AL, Brake BJ, McGiboney DL, Gorman GW, Broome CV. Reactivity of serum from patients with suspected legionellosis against 29 antigens of legionellaceae and *Legionella*-like organisms by indirect immunofluorescence assay. *J Infect Dis* 1983;**147**:23–31.

6 Biberfeld G, Arneborn P, Forsgren M, von Stedingk LV. Non-specific polyclonal antibody response induced by *Mycoplasma pneumoniae* in vitro and in vivo. *Yale J Biol Med* 1984;**57**:893.

7 Vejtorp M, Mansa B. Rubella IgM antibodies in sera from infants born after maternal rubella later than the 12th week of pregnancy. *Scand J Infect Dis* 1980;**12**:1–5.

8 Lind K, Collins MT, Aalund O. Comparison of a microagglutination test and the indirect immunofluorescence test for *Legionella* antibodies in patients. *Acta Pathol Microbiol Immunol Scand [B]* 1984;**92**: 195–9.

9 Biberfeld G, Sterner G. Effect of *Mycoplasma pneumoniae* infection on cell-mediated immunity. *Infection* 1976;**4**(suppl 1):17–20.

Br Heart J 1987;58:296–8

A case of subacute effusive constrictive pericarditis with a probable amoebic aetiology

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SUMMARY A 48 year old man with amoebic pericarditis did not improve after pericardiocentesis. Facilities for echocardiography and haemodynamic studies were not available. Cardiac compression was suspected and at emergency pericardiectomy subacute effusive constrictive amoebic pericarditis was found. The patient recovered.

This is believed to be the first report of a case of subacute effusive constrictive pericarditis caused by amoebiasis.

A 48 year old man was admitted on 14 April 1986 with a one month history of shortness of breath, left chest pain, fever, oedema of the feet, and progressive weakness. On examination he was toxic, febrile, and anaemic and had pedal oedema. His pulse was 110 beats/minute, feeble, and regular; blood pressure was 80/60 mm Hg and a pulsus paradoxus was present. The central venous pressure was 25 cm of saline. The apex beat was not palpable and the first and second heart sounds were feeble. A pleuropericardial rub was also detected. The liver was palpable 8 cm below the right costal margin and was tender.

Routine investigations showed haemoglobin 92 g/l, total leucocytes 18 000/mm^3, erthrocyte sedimentation rate 30 mm/1st h, no abnormality of urine or stool, blood urea 17·85 mmol/l, serum creatinine 176·8 μmol/l; serum total proteins 60 g/l, serum albumin 27 g/l, serum globulin 33 g/l, serum alkaline phosphatase 0·35 μkat/l. Serum electrolytes, concentrations of serum transaminases and serum bilirubin were normal. The chest *x* ray (posterior/anterior view) was suggestive of pericardial effusion, with a cardiothoracic ratio of 0·7. Electrocardiography did not reveal any abnormality. Facilities for echocardiography and haemodynamic studies were not available.

A provisional diagnosis of cardiac tamponade was made and within two hours of admission an emergency pericardiocentesis was performed via the epigastric approach. It yielded 300 ml of anchovy sauce pus. But this did not produce any appreciable change in the patient's pulse, blood pressure, or central venous pressure. There was a slight improvement in symptoms though. The patient was then treated with intravenous fluids, metronidazole, and dehydroemetine.

The next day a liver scan with technetium-99m (phytate) revealed considerable hepatomegaly and a reduced uptake over the upper left lobe and upper medial right lobe. Aspiration of the liver abscess on two occasions, at an interval of two days, yielded 800 ml of anchovy sauce pus. No amoebae were found in the pericardial pus. Medication was continued. There was not much relief of his symptoms and blood pressure remained at 80/60 mm Hg, pulse 120 beats/minute, temperature 38°C, and central venous pressure 24 cm of saline. We then suspected cardiac compression and decided to operate although he was clearly a poor risk patient. At operation 150 ml of anchovy sauce pus under tension was released and we removed the thick parietal and visceral pericardium overlying the ventricles.

Immediately after operation pulse rate settled at 90/min, the blood pressure rose to 110/70 mm Hg, and the central venous pressure fell to 8 cm of saline. A postoperative chest *x* ray showed a normal cardiothoracic ratio. He was treated with digoxin, metronidazole, and blood transfusions. We kept a close watch on him for ten days and he was discharged on 5 May 1986 in good health.

Pathological examination

Histopathological examination of the excised pericardium showed a complete loss of mesothelial cells

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and the surface was covered with a granular exudate containing nuclear debris and a large number of ghost cells with karyolytic nuclei. Beneath this exudate was a layer of fibrin and collagenous tissue. The rest of the tissue showed subepicardial fat containing proliferating fibroblasts and lymphocytic infiltrate. The inflammatory response was not pronounced. No neutrophils could be demonstrated. Although we did not find *Entamoeba histolytica,* we did see occasional structures in the superficial necrotic exudate that appeared to be degenerated entamoebae.

Discussion

At admission this appeared to be a case of cardiac tamponade. Emergency pericardiocentesis produced only partial and temporary relief. Subsequent pericardiectomy yielded 150 ml of anchovy sauce pus under tension. The visceral pericardium was thick and constrictive. After pericardiectomy the patient improved remarkably and remains symptom free. The clinical picture and findings at operation suggest that this was a case of amoebic subacute effusive constrictive pericarditis.

Subacute effusive constrictive pericarditis[1,2] is diagnosed when the right atrial pressure remains raised after the intrapericardial pressure has been reduced to normal by the removal of pericardial fluid. Pericardiocentesis produces only partial or no relief in signs and symptoms. At operation there is extensive thickening of the parietal and visceral pericardium and the free pericardial space contains 100–150 ml of fluid under tension.[1]

The most common causes[3] of subacute effusive constrictive pericarditis are idiopathic[1] or presumed viral pericarditis,[3] tuberculosis,[4] neoplastic infiltration of the pericardium,[5,6] and mediastinal irradiation.[1,7] Other causes are viral,[8] acute pyogenic pericarditis,[9-11] a uraemic[12] and post traumatic pericarditis.[13] Amoebic pericarditis is a rare[14] complication of amoebic liver abscess. We know of no other reports of amoebic pericarditis causing subacute effusive constriction. In a case of pericarditis reported by Kala and Sharma a total of 1500 ml fluid was drained from the pericardial cavity on two separate occasions.[15] Finally their patient had to be treated by pericardiectomy and there was evidence of cardiac constriction. We feel that they too were treating a case of amoebic subacute effusive constrictive pericarditis.

In our case the coexistence of an abscess in the left lobe of the liver together with pericardial effusion suggested an amoebic cause. Although *Entamoeba histolytica* was not found in the pericardial fluid, the absence of acute inflammation in the pericardium and the aspiration of anchovy sauce pus from both the liver abscess and the pericardial sac were considered to be diagnostic of amoebic pericarditis. *Entamoeba histolytica* is rarely demonstrable in the pericardial fluid but the diagnosis can be based on aspiration of anchovy sauce pus from the pericardial cavity.[16]

When amoebic subacute effusive constrictive pericarditis is suspected haemodynamic studies should be performed and if they indicate subacute effusive constriction, pericardiectomy should be performed immediately.[1] If operation is delayed constrictive pericarditis will develop with myocardial infiltration.[13] If there are no facilities for haemodynamic studies management will be determined by the clinical symptoms, pulse, blood pressure, and the central venous pressure. If after pericardiocentesis blood pressure remains low, the central venous pressure does not fall, and tachycardia persists, an underlying cardiac constriction should be suspected. Constriction, if present, will be confirmed at operation, as happened in our case.

References

1 Hancock EW. Subacute effusive-constrictive pericarditis. *Circulation* 1971;43:183–92.
2 Rasaretnam R, Chanmugam D. Subacute effusive constrictive epicarditis. *Br Heart J* 1980;44:44–8.
3 Beverly HL, Braunwald E. Pericardial disease. In: Braunwald E, ed. *Heart disease. A text book of cardiovascular medicine.* 2nd ed. Philadelphia: WB Saunders, 1984:1496.
4 Wood P. Chronic constrictive pericarditis. *Am J Cardiol* 1961;7:48–61.
5 Spodick DH, Kumar S. Subacute constrictive pericarditis with cardiac tamponade. *Dis Chest* 1968;54:62–6.
6 Mann T, Brodie BR, Grossman W, McLaurin L. Effusive-constrictive hemodynamic pattern due to neoplastic involvement of the pericardium. *Am J Cardiol* 1978;41:781–6.
7 Steinberg I. Effusive constrictive radiation pericarditis. Two cases illustrating value of angiocardiography in diagnosis *Am J Cardiol* 1967;19:434–9.
8 Cooper DKC, Sturridge MF. Constrictive epicarditis following Coxsackie virus infection. *Thorax* 1976;31. 472–4.
9 Rubinstein JJ, Goldblatt A, Daggett WM. Acute constriction complicating purulent pericarditis in infancy. *Am J Dis Child* 1972;124:591–4.
10 Scott LP, Knox D, Perry LW, Pineros-Torres FJ. Meningococcal pericarditis; report of two cases, one complicated by acute constrictive pericarditis. *Am J Cardiol* 1972;29:104–8.
11 Ehrich DA, Widmann JJ, Abelmann WH. Acute effusive constrictive Straphylococcal pericarditis.

Chest 1975;67:721–3.
12 Spaulding WB. Subacute constrictive uremic pericarditis. *Arch Intern Med* 1967;119:644–7.
13 Mullen DC, Dillon ML, Young WG Jr, Sealy WC, Durham NC. Pericardiectomy in non-tuberculous pericarditis. *J Thorac Cardiovasc Surg* 1969;58:517–29.
14 Juniper K. Amoebiasis. *Clinics in gastroenterology*. London: WB Saunders, 1978:7:3–29.
15 Kala PC, Sharma GC. Amoebic pericarditis treated by pericardiectomy. *J Indian Med Assoc* 1980;74:194–6.
16 Kulpati DD, Venkatachalam CG, Saha NC. Amoebic pericarditis—a case report. *J Assoc Physicians India* 1976;24:119–22.

Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts was 10 July 1987.

The Annual General Meeting for 1988 will take place in Belfast on 23 and 24 March 1988, and the closing date for receipt of abstracts will be 4 January 1988.

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The Tenth European Meeting of the International Society of Heart Research will be held in Rotterdam on 7 to 9 September 1989. Inquiries to: Office for Post Graduate Medical Education, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

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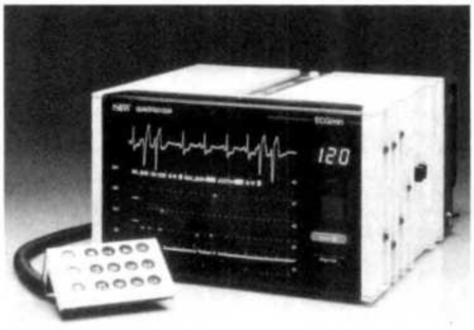

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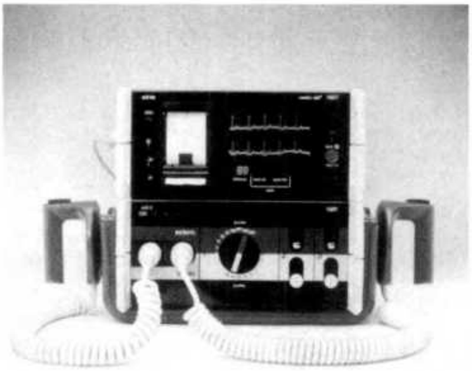

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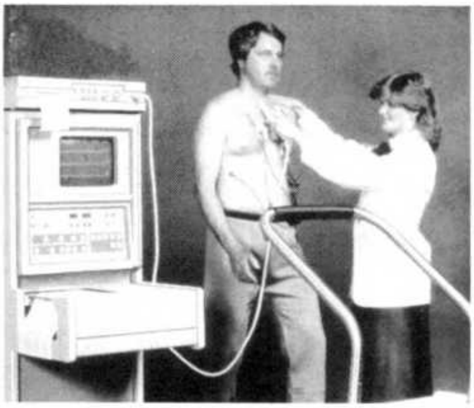

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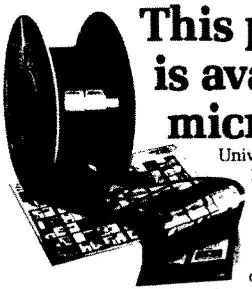

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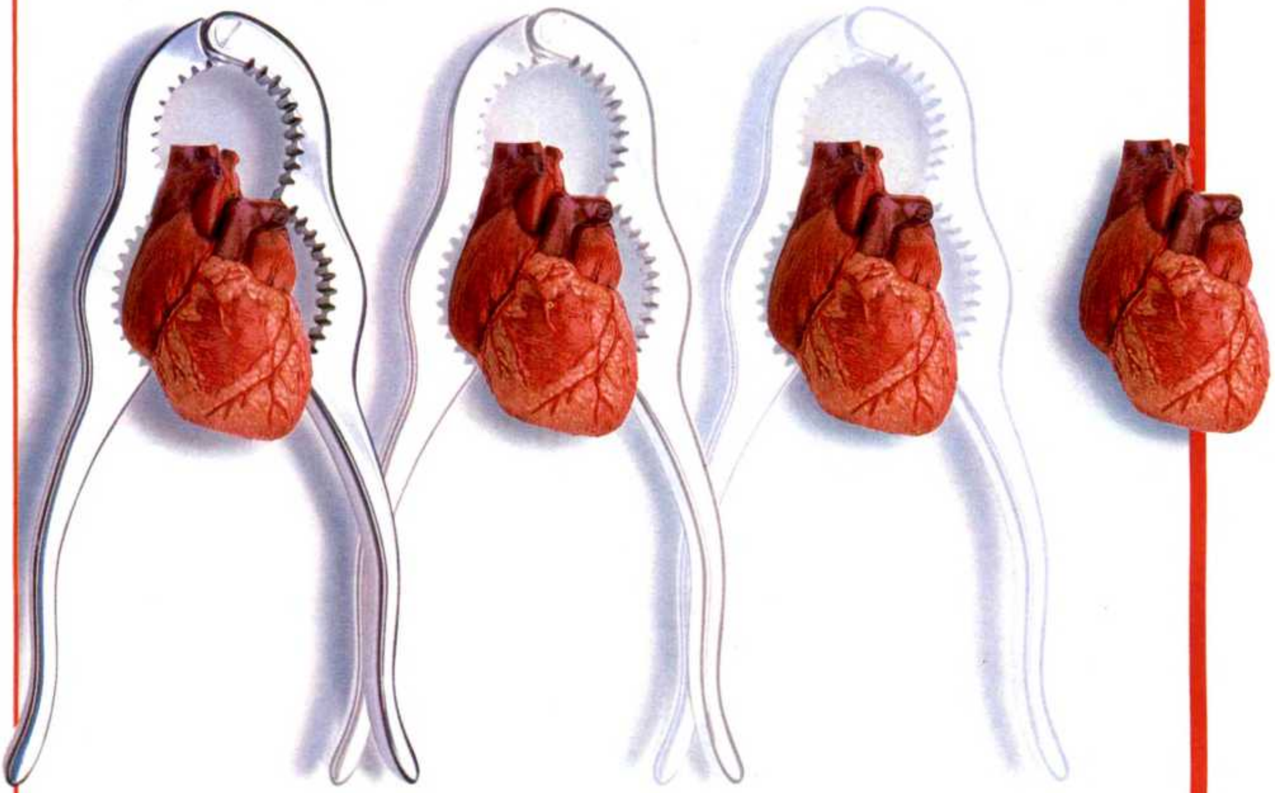

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Br Heart J 1987;58:299–302

Jubilee Editorial

Hypertrophic cardiomyopathy

W BRIGDEN

From the London and National Heart Hospitals, London

When I first used the expression "cardiomyopathy" in 1956 I did not realise that I had coined a term that would become widely applied. Experience, however, has confirmed its value in describing isolated non-coronary, non-hypertensive, and non-valvar myocardial disease, especially when used with an adjective if the aetiology or morphology is sufficiently clear. Some authorities prefer to restrict its use to disorders of the myocardium of unknown cause; this would exclude hypertrophic cardiomyopathy which in most patients is an inherited disorder. Although the division into hypertrophic and congestive cardiomyopathies has proved helpful, classification remains somewhat unsatisfactory despite many worthy attempts to clarify the position.

Unexplained and isolated myocardial hypertrophy was described in the nineteenth century by German pathologists and an obstructive element was recognised in their reference to "conus stenosis". Two patients with massive hypertrophy were reported in 1907 by Schminke who considered that hypertrophy led to further hypertrophy.[2] Several papers were published in the 1930s and 1940s under various titles describing isolated myocardial hypertrophy, and Evans's paper on "familial cardiomegaly" in the *British Heart Journal* was particularly important.[3] He described nine patients seen at the London Hospital and emphasised the diagnostic importance of a family history of similar disease, frequent arrhythmias, and a tendency to sudden death. Brock later added another facet to the story in suggesting the possibility that hypertrophic muscle was responsible for obstruction.[4] He had observed and was impressed by apparent obstruction of the outflow tract by hypertrophic muscle after pulmonary stenosis had been relieved by valvotomy and he later described apparently important muscular obstruction in the left ventricle. Teare, a forensic pathologist, followed with a description, also in the *British Heart Journal*, of asymmetric septal hypertrophy found at necropsy in seven subjects who had died suddenly.[5]

Thus the strands of medical knowledge were converging and pointing to a distinct disease entity that was characterised by an apparently idiopathic isolated and often asymmetric myocardial hypertrophy, possibly obstructive, occurring in families, and with a tendency to cause sudden death. A spate of papers followed in the early 1960s describing the clinical, electrocardiographic, angiographic, and haemodynamic features of this condition. Contributions from Braunwald and his colleagues at the National Institutes of Health, Bethesda[6 7] and from Goodwin and colleagues at Hammersmith Hospital[8–10] were most important, but they used different names—idiopathic hypertrophic subaortic stenosis in the United States and hypertrophic obstructive cardiomyopathy in the United Kingdom. Neither term recognised the familial factor and both emphasised obstruction which often is not present. McMichael found 12 names for this condition in 1964[11]; I think there were more, illustrating the principle that the number of names is directly related to the obscurity of the condition.

Criley and others criticised the concept of obstruction on various grounds including the evidence of striking dynamic lability, the effective rapid discharge of ventricular volume in early systole, and the low end systolic volume, even in some of the most severe cases.[12] These points, however, do not deny an obstructive element because coexistent mitral reflux could explain these findings. The triad of cardiac pain, faintness or syncope on exertion, and dyspnoea on exertion in patients who have severe disease certainly suggests obstruction, especially when combined with large intraventricular gradients, albeit variable and of functional origin. Very large gradients seem to be associated with early mitral-septal contact. I find the argument about obstruction a specious one. In this disease, however, the array of symptoms, unlike the signs, does not

Requests for reprints to Dr W Brigden, 45 Wimpole Street, London W1M 7DG.

closely match the abnormal morphology and dynamic function. Most cardiologists have been more impressed by the haemodynamic abnormalities caused by abnormal diastolic filling than by the abnormal systolic features of the condition. I have seen a patient with hypertrophic cardiomyopathy develop a paroxysm of atrial fibrillation resulting in profound hypotension and syncope followed by recovery with the spontaneous restoration of sinus rhythm. The paralysis of atrial transport by fibrillation assumes great importance in patients with thick stiff ventricles and may cause severe hypotension and even syncopal death.

Abnormal signs

Abnormal signs range from none in the mild symptom free case to those which closely reflect abnormal dynamic function. Diastolic dysfunction is underlined by finding the physical signs of vigorous atrial systole, such as a prominent "a" wave in the jugular venous pulse or a short low-pitched diastolic murmur enhanced by inspiration from impeded tricuspid inflow. I remember a discussion at the National Heart Hospital nearly thirty years ago about a child who appeared to have severe tricuspid stenosis and strange unexplained left ventricular hypertrophy. Eponyms abounded, including Bernheim and Ebstein, to explain the findings which included giant atrial P waves. Subsequent necropsy showed gross septal hypertrophy and normal valves. Systolic murmurs, most commonly in late systole though not engulfing the aortic second sound, often led to an erroneous diagnosis of aortic valve stenosis or even mitral reflux. On the other hand, the occasional truly late systolic murmur or pansystolic murmur caused by mitral reflux was thought to be of valvar origin. It is thus not surprising that this condition was only recognised by clinicians some 25 years ago—in view of its pleomorphic presentation and mimicry of so many other kinds of heart disease.

Arrhythmias

Arrhythmias are common and the tachycardias particularly so. Frequent ventricular extrasystoles and ventricular tachycardias may presage sudden death. On the other hand, prolonged phases of such disturbance may be followed by a slow spontaneous regression to periods free of arrhythmia; nevertheless, frequent ventricular arrhythmias should be suppressed by appropriate medication in view of their association with deterioration or sudden death. A galaxy of rhythms was recorded over some ten years in one of my patients who first presented at the age of 15 with apparently simple idiopathic paroxysmal tachycardia, but three years later a firm diagnosis of hypertrophic cardiomyopathy was made when ventricular extrasystoles were frequent; and in her mid twenties asymptomatic complete heart block developed.

Echocardiography

The development of echocardiography in the 1960s stimulated further research and proved to be of considerable diagnostic value, enabling wall thickness and movement as well as valve motion to be assessed and studied seriatim. Some overdiagnosis occurred, as is usual with new tools in biological research. The strange systolic movement of the anterior mitral valve cusp has proved of diagnostic value and added credibility to the angiographic appearance of outflow obstruction caused by apposition of the mitral leaflet and septum. The mechanism of this movement remains obscure and although a Venturi effect is possible abnormal dynamic function of thick papillary muscle seems more likely. Premature closure of the aortic valve may be seen and is clearly related to rapid early ejection ending at the time of mitral-septal contact. Echocardiograms are valuable for studying apparently unaffected relatives of a propositus and have shown that mild forms of cardiomyopathy are not uncommon and are consistent with leading a normal life. Echocardiography enhances, but certainly does not replace, clinical assessment in this condition any more that it does in any other disease.

Genetic origin

Genetic origin of hypertrophic cardiomyopathy is now widely accepted and almost all clinical accounts describe a familial nature that is sometimes traceable through several generations. Echocardiography has enabled the assessment of relatives by a test that is not only non-invasive but also is sometimes positive when electrocardiograms and *x*-rays are equivocal or even normal. Elegant studies on the familial nature of the disease by Emanuel and colleagues have confirmed the autosomal dominant nature of its inheritance.[13–14] They also showed that current techniques for detecting the disease might not give positive results before early adult life. There are sporadic cases that fulfil all the criteria for diagnosis but these do not deny a genetic aetiology. The percentage of isolated cases in any series in likely to be erroneously high for many reasons. A simple negative response when inquiries are made of the patient's family must be queried, especially if relatives have died unexpectedly, because there is an understandable tendency to withhold disquietening information from younger, apparently healthy members. Adoption unknown to one of my patients whose real mother had died in the puerperium was the reason for negative information, and another "sporadic" case subsequently had an affected child. Possibly some sporadic cases are caused by a recessive gene.

Pathology

The pathology of this condition has been extensively described and discussed during the past three decades. The distribution of hypertrophy may be generalised or regional (commonly in the anterior basal part of the septum or rarely confined to the free wall). Although morphology correlates well with dynamic function and physical signs, gross appearances do not correlate closely with symptoms in this condition. There should be no dispute about facts, but pathologists like clinicians tend to disagree about their interpretation. I refer to the specificity, or otherwise, of the myocardial disarray that is found in almost all cases. It seems that some minor degree of disarray occurs in secondary hypertrophy and this sign is therefore not specific, but in hypertrophic cardiomyopathy there is very extensive disorganisation of large muscle bundles as well as disarray between fibres and small whorls of muscle; furthermore there is even disorganisation of fibrils within a single cell. Organ abnormality such as visceromegaly, congenital defects, and evidence of endocrinopathy, other than as an effect of heart failure or embolism, are conspicuously absent at necropsy. There have been, however, a few reports of a familial hypertrophic cardiomyopathy associated with a mitochondrial abnormality affecting skeletal muscle.

Treatment

Treatment is essentially unsatisfactory because so far the hypertrophic process has not been reversed, but symptoms and possibly the course of the disease may be modified favourably. The great variation in symptoms and severity of this condition demands the tailoring of treatment to the individual patient. The β blockers became generally available at about the same time as the disease became more widely recognised; and in the early sixties these agents seemed heaven-sent. Here was a drug that would slow the heart, reduce contractility, and block the apparently excessive catecholamine drive. Although β blockers have not fulfilled that early promise in hypertrophic cardiomyopathy, nevertheless, propranolol may relieve or greatly reduce some symptoms, especially cardiac pain, in at least 50% of patients and so it remains the drug of first choice except when arrhythmias are a prominent feature. Amiodarone, unlike the calcium antagonists and β blockers, is remarkably effective in reducing the frequency and impact of both ventricular and supraventricular tachycardia. There is some evidence that amiodarone together with the cautious addition of a low dose β blocker is better than either alone in controlling symptoms in the most severely affected patients. Heart failure should not be treated with drugs which lower systemic pressure by vasodilatation because this will increase the obstructive factor; also diuretics should only be used with caution.

Surgical treatment

Surgical treatment by myotomy or myomectomy was, like the β blockers, introduced in the early 1960s. There is general agreement that operation should be restricted to those patients with severe symptoms that are unresponsive to medical treatment and with evidence of a large outflow tract gradient. The immediate surgical mortality is high and congestive cardiac failure is not uncommon in the late postoperative period. Severe mitral reflux may develop in hypertrophic cardiomyopathy and should be treated by valve replacement. The results are not as satisfactory as in primary valve disease. But, not surprisingly, outflow tract gradients are abolished and symptoms are sometimes improved.

Course

The course of this disease is ill defined and extremely variable, hence prognosis is particularly difficult. Death is often unexpected and its suddenness a cause for comment in most accounts of the disease over the past thirty years. Those patients with a family history of sudden death and evidence of ventricular arrhythmias are certainly at great risk of syncopal death. It is of interest, however, that not all sudden death in this disorder is caused by arrhythmia. On the other hand, some symptom free patients with minimal disease achieve a normal life span. I have seen symptom free but quite severe hypertrophic myopathy in a patient in his seventies, restricting symptoms in a patient of seven, and unexpected death at the age of eleven. Congestive heart failure often associated with atrial fibrillation may develop in those who survive with a long history of severe disease. Outflow tract gradients then tend to diminish and morphologically there may be patchy thinning of the hypertrophic myocardium, possibly caused by infarction or fibrosis in areas of reduced perfusion; thus in the late stages a differential diagnosis between this extraordinary disorder and non-hypertrophic cardiomyopathy may prove very difficult.

The ever increasing knowledge of disease continually reveals new problems and thus widens the scope of our ignorance. Hypertrophic cardiomyopathy is no exception, since the capacity of a highly specialised tissue such as myocardium to grow beyond its allotted size is as remarkable a biological phenomenon as the timely cessation of normal growth. When increased resistance to contraction is the stimulus for myocardial hypertrophy the result is mostly homoeostatic and comprehensible, but what of apparently purposeless and almost chaotic hypertrophy? We know that there is usually a genetic fault but we know nothing of its origin or of its translation into pathogenesis. It is not surprising therefore that we have not yet found a means of reversing this extraordinary disorder.

References

1 Brigden W. Uncommon myocardial disease—the non coronary cardiomyopathies. *Lancet* 1957;**ii**:1179–84, 1243–9.
2 Schminke A. Muskulose Conusstenosen. *Dtsch Med Wochenschr* 1907;**33**:2082–5.
3 Evans W. Familial cardiomegaly. *Br Heart J* 1949;**11**:68–82.
4 Brock RC. Functional obstruction of the left ventricle. *Guy's Hosp Rep* 1957;**106**:221–38.
5 Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J* 1958;**20**:1–8.
6 Braunwald E, Morrow A, Cornell W, Aygen M, Hilbish TF. Idiopathic hypertrophic aortic stenosis. *Am J Med* 1960;**29**:924–45.
7 Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis, clinical analysis of 106 patients. *Circulation* 1968;**37**:759–88.
8 Goodwin JF, Gordon H, Holman A, Bishop M. Clinical aspects of cardiomyopathy. *Br Med J* 1961; **i**:69–79.
9 Swan DA, Bell B, Oakley CM, Goodwin J. Analysis of symptomatic course and prognosis and treatment of hypertrophic obstructive cardiomyopathy. *Br Heart J* 1971;**33**:671–85.
10 Goodwin JF. The frontiers of cardiomyopathy. *Br Heart J* 1982;**48**:1–18.
11 McMichael J. *Cardiomyopathies. Ciba Foundation symposium.* London: J and A Churchill, 1964.
12 Criley J, Lewis K, White R, Ross R. Pressure gradients without obstruction: a new concept of hypertrophic subaortic stenosis. *Circulation* 1965;**32**:881–7.
13 Emanuel R, Withers R, O'Brien K. Dominant and recessive modes of inheritance in idiopathic cardiomyopathy. *Lancet* 1971;**ii**:1065–7.
14 Feizi O, Emanuel R. Echocardiographic spectrum of hypertrophic cardiomyopathy. *Br Heart J* 1975; **37**:1286–1302.

Br Heart J 1987;58:303–5

Editorial

Valve prostheses and pregnancy

CELIA OAKLEY

From the Department of Clinical Cardiology, Hammersmith Hospital, London

All patients with mechanical heart valves need long term treatment with anticoagulant drugs to prevent thromboembolism. Because the use of these drugs in pregnancy increases the risk of abortion or fetal damage management of pregnant women with valve prostheses is still controversial. Women with artificial heart valves may even be advised against pregnancy because of the "serious risks to both mother and child".[1]

A hypercoagulable state exists in pregnancy when concentrations of clotting factors, platelet turnover, and viscosity are increased and fibrinolysis is diminished. These changes increase the risk of prosthetic valve thrombosis.[2]

Whenever possible childbearing should be completed before valve replacement. In general, patients with severe mitral or aortic regurgitation tolerate pregnancy well probably because of the beneficial effects of vascular dilatation; the slight increase in heart rate seen in most pregnancies will limit aortic regurgitation. Patients with mitral stenosis suitable for valvotomy should have this carried out before pregnancy. For suitable valves closed mitral valvotomy during pregnancy can be successful without increased hazard to either mother or fetus if operation is avoided during the first trimester. This avoids prolonged admission to hospital with the adverse effects on the marriage and also ensures that the mother will be in good health to look after the infant and her family. Unfortunately, few surgeons in the developed world are now trained to do closed mitral valvotomy and risk of fetal loss when the operation is performed under bypass is considerable; however, many such operations have been performed successfully. Patients with mitral stenosis in sinus rhythm who are unsuitable for valvotomy or who have severe aortic stenosis (fortunately a rare condition) may be helped through pregnancy with β blockers.

Fitness for pregnancy depends on the woman's general health and haemodynamic reserve; the reason for the valve replacement (such as Marfan's syndrome with its special maternal and genetic risk); the possible effects on fetal development of drugs given to the mother; the risk of thromboembolism, arrhythmia, or infection; and the maternal prognosis. Most patients with mitral or aortic valve replacements, even double or triple valve replacements for rheumatic heart disease, tolerate pregnancy well. Most such young patients are in New York Heart Association classes I or II, but a few may be in class III or IV and will be at increased risk. A full echocardiographic study should be carried out to evaluate left ventricular and valvar function and consolidate the clinical assessment. When there is doubt, an exercise test provides a valuable indication of the cardiac reserve.

Anaemia caused by menorrhagia is common when anticoagulants are being taken, and mechanical haemolysis may add to the risk of anaemia—although this is rare with modern valves unless there is a paraprosthetic leak. Patients with rheumatic valve disease may develop atrial fibrillation in pregnancy and if this occurs the rate should be brought under rapid control with digoxin and a β blocker. Cardioversion can be carried out in pregnancy and does not induce ventricular fibrillation in the fetus. Other antiarrhythmic drugs that can be used safely are verapamil, quinidine, and disopyramide. If a diuretic is needed the dose should be kept to a minimum and adjusted to the pulmonary rather than the systemic venous pressure. Patients with mitral valve prostheses tend to have a raised venous pressure in pregnancy, particularly if atrial fibrillation is present.

Because rheumatic fever is now rare in developed countries, experience of large numbers of pregnancies in women with artificial heart valves is more often reported from the Third World than from the West.[1 3-5] Most of the patients have mitral valve prostheses and just over a third of such patients in a recent report from Mexico were in atrial fibrillation.[1]

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In the early years of experience with porcine xenografts and other "tissue" valves, their use was advocated in young women who might wish to become pregnant.[6] Unfortunately, the long term durability of these valves is disappointing, particularly in the young[7] and valve deterioration is likely to be especially rapid in pregnancy. The certain need for reoperation and the risk of between 5% and 10% for each operation make the use of tissue valves in the young unjustifiable. In any case the commonest condition requiring valve replacement in young women is rheumatic mitral valve disease in which an enlarged left atrium, previous thromboembolism, or atrial fibrillation impose an absolute need for long term anticoagulant treatment whatever kind of valve is implanted.

Coumarin derivatives carry a teratogenic risk of chondrodysplasia with nasal hypoplasia, optic atrophy, and dwarfism when they are administered between the sixth and ninth week of gestation.[1 4 8 9] The fetus becomes overanticoagulated because warfarin but not vitamin K dependent coagulation factors cross the placenta and the immature fetal liver is more sensitive to the anti-vitamin K effect of the drug. Neurological complications which have occurred after the administration of coumarin later on in pregnancy are almost certainly attributable to haemorrhage. This risk is further increased at delivery.

The antiplatelet agents, aspirin and dipyridamole, do not prevent thromboembolism from prosthetic valves in non-pregnant patients and they are even less effective during pregnancy when the mother is at increased risk of systemic embolisation.[2 4 10]

Because heparin is a large molecule that does not cross the placenta and can have no teratogenic or anticoagulant effect on the fetus, it has been suggested for use during pregnancy either in prophylactic doses[4] or for full anticoagulation employing a heparin lock, self-administration, and with the aim of achieving a partial thromboplastin time of 1·5–2·0 × normal.[11] The suggestion that heparin should be started before conception[11] means that some women could remain on treatment indefinitely.

Hall *et al* reviewed 135 published cases in which heparin had been given during pregnancy to patients with artificial valves.[12] The details of administration were not always clear but most were probably treated with subcutaneous heparin. Since either success or failure may stimulate reporting, such reviews may not give a true picture, but Hall found that an eighth of the infants were stillborn, a fifth were premature (a third of whom died), and only two thirds were normal—about the same success rate which followed the use of coumarin derivatives throughout pregnancy. Maternal haemorrhage occurred in 14 (10%) of the patients and there were three deaths (2%). The high fetal loss was attributable to retroplacental haemorrhage. Wang *et al* reported four abortions in 10 patients given subcutaneous heparin in the first trimester.[13]

As a compromise it has been suggested that the coumarins should be replaced by subcutaneous heparin during the first trimester and the last two weeks of pregnancy. An early report by Salazar *et al* of the use of heparin in a fixed dose of 5000 units every 12 hours was encouraging.[4] More recently, his group examined the risk of embryopathy when coumarins were given throughout pregnancy, when heparin was given from the 6th to 12th week, and when heparin was started after the seventh week. The high incidence of spontaneous abortion was similar with all three regimens, but two women receiving subcutaneous heparin during the first trimester suffered massive valve thombosis and in another the valve thrombosed during the last two weeks of pregnancy after the patient had been transferred back to heparin.

Children were examined for signs of embryopathy by a clinical geneticist and this probably explains why the reported incidence was higher than in other reports.[12 14] No abnormalities were seen in any of the children born after heparin had been used from the sixth week but two out of eight of the liveborn infants resulting from the 12 pregnancies treated with heparin between the 7th and 12th weeks had suggestive minor facial defects and two out of 27 children resulting from 37 pregnancies in women receiving coumarin drugs throughout pregnancy had features of embryopathy. No cases of central nervous system defects, dwarfism, or epiphyseal stippling were seen, however, so none of these children was seriously affected. Chen saw no cases of embryopathy among 22 pregnancies in which the mothers continued warfarin throughout the first trimester.[3]

None of the 54 children studied in the Mexican series had defects such as microcephaly or spasticity attributable to the use of coumarin anticoagulants during the last two trimesters of pregnancy.[1]

The sum of the recently reported experience suggests that a successful outcome can be expected in about two thirds[6] of cases when coumarin derivatives are used throughout pregnancy.[3 6 12] The risk of a liveborn child having a disabling coumarin embryopathy seems to be $<5\%$.

There are many published reports of valve thrombosis in mothers receiving heparin.[1 13–17] This has occurred mainly, but not invariably in Björk-Shiley valves and usually after heparin prophylaxis, but there has been one report in a patient with a Starr mitral prosthesis who was on anticoagulant doses of heparin.[16]

The use of anticoagulant doses of heparin may reduce the risk of valve thrombosis (though this has still to be shown), but it carries a substantial risk of both maternal haemorrhage and spontaneous abortion. Moreover, it can also cause thrombocytopenia, alopecia, and osteoporosis.[17 18]

Intravenous heparin has been widely used in hospital in the last two weeks of pregnancy without adverse effects. It has the virtue that both the mother and the fetus can be continuously observed. The effect of warfarin on the baby must be assumed to persist for seven to ten days after warfarin is stopped and the baby should be given vitamin K. Breast feeding is not contraindicted.[19] If the mother is admitted in premature labour while still on warfarin she should be given fresh frozen plasma before caesarean section. The effects of heparin can be temporarily reversed with protamine, and warfarin treatment can be resumed immediately after delivery.

It is uncertain whether the teratogenic effect of coumarin derivatives is the result of their chemical structure or of the anticoagulant effect exerted at a critical period of development of cartilagenous bone. The lack of information about the safety of phenindione during the first trimester may be attributable to its infrequent use rather than to its greater safety. Nevertheless, at Hammersmith Hospital we have for some years transferred young women to phenindione in pregnancy and have had no embryopathies and no compromised babies.[20]

Although both Hall and Salazar concluded that women of childbearing age with artificial valves should be advised not to attempt pregnancy, we are more optimistic[21 22] and believe that the danger to the mother is very small[6]; that the chance of a successful outcome is good; and that most unsuccessful pregnancies are miscarried so that the risk of a liveborn malformed baby is small. Whenever possible, childbearing should be completed before valve replacement, but when this is not possible, mechanical valves should be chosen and currently phenindione is the preferred anticoagulant with transfer to intravenous heparin in hospital during the last two weeks of pregnancy.

References

1 Iturbe-Alessio I, Fonseca M, Mutchinik O, Santos MA, Zajarias A, Salazar E. Risks of anticoagulant therapy in pregnant women with artificial heart valves. *N Engl J Med* 1986;**315**:1390–3.

2 Schaffer AT. The hypercoagulable states. *Ann Intern Med* 1985;**102**:814–28.

3 Chen WWC, Chan CS, Lee PK, Wang RYC, Wong VCW. Pregnancy in patients with prosthetic heart valves: an experience with 45 pregnancies *Q J Med* 1982;**51**:358–65.

4 Salazar E, Zajarias A, Gutierrez N, Iturbe I. The problem of cardiac valve prostheses, anticoagulants and pregnancy. *Circulation* 1984;**70** (suppl 1):1.169–77.

5 Ben Ismail M, Abid F, Trabelsi S, Taktak M, Fekih M Cardiac valve prostheses, anticoagulation, and pregnancy *Br Heart J* 1986;**55**:101–5.

6 Oakley C, Doherty P. Pregnancy in patients after valve replacement *Br Heart J* 1976;**38**:1140–8.

7 Magilligan DJ Jr, Lewis JW Jr, Tilley B. The porcine bioprosthetic valve. Twelve years later. *J Thorac Cardiovasc Surg* 1985;**89**:499–507.

8 Ibarra-Perez C, Arevalo-Toledo N, de la Cadena AO, Noriea-Guerra L. The course of pregnancy in patients with artificial heart valves. *Am J Med* 1976;**61**.504–12.

9 Stevenson RE, Burton OM, Firlanto GS, Taylor HA. Hazards of oral anticoagulants during pregnancy. *JAMA* 1980;**243**·1549–51.

10 Biale Y, Cantos A, Lewen Thal H, Gueron M. The course of pregnancy. patients with artificial heart valves treated with dipyridamole. *International Journal of Obstetrics and Gynaecology* 1980;**81**:128–32.

11 Chesebro JH, Adams PC, Fuster B. Antithrombotic therapy in patients with valvular heart disease and prosthestic heart valves. *J Am Coll Cardiol* 1986;8.41–56B.

12 Hall JG, Paull RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980;**68**:122–40

13 Wang RYG, Lee PK, Chow JF, Chen WWC. Efficacy of low dose, subcutaneous administered heparin in treatment of pregnant women with artificial heart valves. *Med J Aust* 1983;**ii**:126–8.

14 De Swiet M. Prescribing in pregnancy: anticoagulants. *Br Med J* 1987;**294**·428–30.

15 Larrea JL, Nunez L, Reque JA, Aguado M, Matarros R, Minguez JA. Pregnancy and mechanical valve prostheses. a high-risk situation for the mother and the fetus. *Ann Thorac Surg* 1983;459–63.

16 Bennett GG, Oakley CM. Pregnancy in a patients with a mitral valve prosthesis. *Lancet* 1968;**ii**:616–9.

17 Chong BH, Pitney WR, Castaldi PA. Heparin induced thrombocytopaemia: association of thrombotic complications with heparin-dependent 1 of G antibody that induces thromboxane synthesis and platelet aggregation. *Lancet* 1982;**ii**:1246–8.

18 De Swiet M, Dorrington Ward P, Fidler J, *et al.* Prolonged heparin therapy in pregnancy causes bone demineralization (heparin induced osteopemia). *Br J Obstet Gynaecol* 1983;**10**:1129–34.

19 Baty JD, Breckenridge A, Lewis PJ, *et al.* May mothers taking warfarin breast feed their infants? *Br J Clin Pharmacol* 1976;3:969

20 Oakley CM, Hawkins DF. Pregnancy in patients with prosthetic heart valves. *Br Med J* 1983;**287**:358.

21 Anonymous. Anticoagulants and heart valve replacement in pregnancy. *Br Med J* 1977;**i**:1047–8.

22 Oakley CM. Pregnancy in patients with prosthetic heart valves. *Br Med J* 1983;**286**:1680–2.

Br Heart J 1987;58:306–15

Review

Da Costa's syndrome or neurocirculatory asthenia

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SUMMARY The syndrome variously called Da Costa's syndrome, effort syndrome, neurocirculatory asthenia, etc has been studied for more than 100 years by many distinguished physicians. Originally identified in men in wartime, it has been widely recognised as a common chronic condition in both sexes in civilian life. Although the symptoms may seem to appear after infections and various physical and psychological stresses, neurocirculatory asthenia is most often encountered as a familial disorder that is unrelated to these factors, although they may aggravate an existing tendency. Respiratory complaints (including breathlessness, with and without effort, and smothering sensations) are almost universal, and palpitation, chest discomfort, dizziness and faintness, and fatigue are common. The physical examination is normal. The aetiology is obscure but patients usually have a normal life span. Reassurance and measures to improve physical fitness are helpful.

Da Costa's syndrome or neurocirculatory asthenia has a long and honourable history in the medical literature and in clinical medicine. Yet it is infrequently mentioned today. It is unlikely to have disappeared; it probably exists much as before but is more often identified and labelled in psychiatric terms such as "anxiety state" or "anxiety neurosis". There is no harm in this shift in diagnostic labels as long as the essential importance of the syndrome, its prognosis, and treatment are properly appreciated. Such is not always the case and, as in other medical issues, it is educational to review and summarise the past. What has been forgotten should not necessarily remain forgotten.

For the purposes of this discussion, a broad definition of Da Costa's syndrome that is applicable to military and civilian patients is: a disorder of unknown origin, often familial, characterised by the presence of one or more symptoms including breathlessness with and without effort, palpitation, nervousness, chest discomfort not typical of angina pectoris caused by ischaemic heart disease, fatigability, and faintness; tending to occur in attacks which may recur over years and for which there is no specific treatment.

Although Jacob M Da Costa is the name most honoured by history in this condition, at least one other relevant report antedated his paper in 1871. On 3 June 1863 Dr Henry Hartshorne made a presentation regarding heart disease in the Union Army to the College of Physicians in Philadelphia. He commented: "Among the chronic affections of soldiers, which are best studied in hospitals remote from the field, is one which does not seem to have met, as yet, with full appreciation by medical officers, inspectors and pension surgeons . . . The affection to which I allude may be designated as *muscular exhaustion of the heart*."[1]

Dr Hartshorne went on to mention that Dr Alfred Stillé had delivered an address on a somewhat similar disorder, referred to by him as "palpitation", before the Philadelphia County Medical Society four months earlier.[2] Stillé had noted that this palpitation was "a very frequent symptom among the soldiers, occurring in perhaps every case of intercostal neuralgia, but often, also, originating apparently in a state of extreme exhaustion . . ." Hartshorne described how in an 80 bed ward of a Union army hospital over a seven month period the majority of the cardiac patients exhibited neither hypertrophy nor dilatation, or palpitation "from sympathy with irritated stomach, from nervousness, abuse of tobacco, etc", but cardiac muscular exhaustion. This was demonstrated by shortness of breath after moderate exertion and a rapid pulse on slight effort. The men appeared well and there were no

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cardiac murmurs; however, sometimes the first heart sound was diminished. Although there was improvement with several months of rest this did not cure most of the cases. He considered that the process was attributable to the stress of the military campaigns with "great and prolonged exertion with the most unfavorable conditions possible—privation of rest, deficient food, bad water, and malaria."

Four year later in February 1867, Dr W C Maclean, who was Professor of Military Medicine at the British Army Medical School, wrote a lecture entitled "Diseases of the heart in the British Army", which was published in the *British Medical Journal*.[3] His message regarding British soldiers was different from that of Hartshorne because he was calling attention to cardiac hypertrophy and dilatation caused, he considered, by excessive exertion from carrying the soldier's field pack, which amounted to over 60 pounds, and by the manner in which its straps constricted the circulation. No symptoms are described in Maclean's paper and it hardly belongs in this historical sequence started by Hartshorne, although both were concerned with the role of physical exhaustion.

The first major publication on the topic was entitled "On irritable heart: a clinical study of a form of functional cardiac disorder and its consequences" by Dr Jacob M Da Costa, published in the January 1871 issue of the *American Journal of Medical Sciences*.[4] Da Costa was only one of a series of notable physicians to be intrigued by this problem, which over the next 70 years included some of the great names in internal medicine.

Da Costa was born in 1833 on the Island of St Thomas in the West Indies. He was educated in Europe and came to Philadelphia in 1849, where at the age of 16 he entered Jefferson Medical College. He graduated three years later at 19 and went on to enrich his education with 18 months of observation in the clinics of Paris and Vienna before returning to practise in Philadelphia. Wooley reviewed his distinguished career,[5] which included publication in 1864, when Da Costa was only aged 31, of a volume on medical diagnosis which was so successful that it ran to nine editions and was translated into German, Russian, and French. Da Costa was appointed to the position of Chairman of Medicine at Jefferson Medical College, was elected President of the College of Physicians of Philadelphia, and was selected as one of the original members and later president of the Association of American Physicians.

Da Costa's role in military medicine came during the Civil War when Philadelphia became the site of several military hospitals. Da Costa was assigned to one at a suburban Philadelphia estate on Turner's Lane. Here Da Costa was exposed to a "cardiac malady common among soldiers". He wrote a report about it to the War Department as early as December 1862 and finally summarised his thoughts in the 36 page article published in 1871 in the *American Journal of Medical Sciences*.[4]

Da Costa's clear description of this malady was supplemented by several case histories. Although the story he tells related only to soldiers, he made the point in the first paragraph that "Much of what I am about to say I could duplicate from the experience of private practice." Therefore, this was not a phenomenon seen solely in military surroundings. Later in the article he confirmed this by mentioning that some of his patients had experienced typical symptoms before enlisting. After commenting that he had chosen the name of "irritable heart" for this "peculiar form of functional disorder", which he believed had also occurred in British troops earlier in the century, he made the following observations.

The condition often followed a period of hard service in the field or a febrile illness with or without diarrhoea; less frequently it was seen after various situations including battle wounds and scurvy. The main symptoms were palpitation with a rapid pulse, with and without effort, and on occasion with slight irregularities; chest pain near the cardiac apex either sharp and lancinating, or dull in character, coming with and without effort; and shortness of breath, again not necessarily associated with exertion. A range of digestive complaints was also common. The physical examination was described as not remarkable except for the unusually rapid pulse, a quick cardiac impulse, and sometimes apical systolic murmurs. Treatment was prolonged and included rest and digitalis preparations, at times combined with aconite or other drugs. A few patients could return to full duty when they had completely recovered, but most had to be assigned light duty or were retired from the service. Da Costa made the point that one infrequent outcome was the development of cardiac hypertrophy, which he believed to have developed in 28 of 200 cases seen. Finally, he cautioned that such a condition occurs with "severe or protracted" military campaigns, and he urged adequate physical training for new recruits, avoidance of forced marches, and provision for adequate convalescence for those with acute infections before they returned to duty.

Such were the features of Da Costa's syndrome as set out in 1871. It must be borne in mind that on the one hand, some of the patients indeed did have or had had malaria, typhoid, acute gastroenteritis, scurvy, malnutrition, and physical exhaustion, and had a reason for temporary asthenia, and Da Costa considered these in his description. And on the other hand, a few others may have had organic heart disease that was undiagnosable at the time, including coronary or hypertensive heart disease, myocarditis, and myocardiopathy. Rheumatic and syphilitic heart disease would probably have been diagnosed. Discounting these, there was left a vivid picture of a residual group with Da Costa's "cardiac malady" which is something else apart—an entity of uncertain origin, consistent clinical features, and disabling but not life threatening consequences.

Although the next major contributions in this area came during the first world war, there were minor evidences of interest from time to time in intervening years. The British authorities did alter the weight and strappings of the soldiers' packs and later altered training drills in futile attempts to prevent the problem from occurring in the troops. (Howell has recently written an excellent review of the British military experience with this syndrome.[6]) The condition is said to have been encountered during military operations in South Africa and India.

The first world war saw an amazing degree of concern for the syndrome described by Da Costa. Some of the best medical brains in Britain were recruited to study the problem. The reason for the mobilisation of all this scientific talent was the extent of Da Costa's syndrome in the allied military forces, which became apparent during the first months of the war. Alfred E Cohn wrote that as of 31 August 1918, 41 699 men had been discharged from the British Army because of heart disease, "most of them probably" because of Da Costa's syndrome.[7] The German army seems to have had a similar experience. Goldscheider reported to the Medical Society of Berlin in 1915 on the frequency in the troops of symptoms referable to the heart due to muscular and nervous exhaustion.[8] He cited no statistics. In 1916 *Archives des Maladies du Coeur* contained a review of 23 published reports of cardiac problems in wartime, many of which resembled Da Costa's syndrome; 10 of the articles cited were German.[9]

As early as 1915, the British Medical Research Committee had arranged for study of "disorders of the soldier's heart" under the general direction of Sir James Mackenzie at University College Hospital in London. Later, an advisory committee was appointed including Mackenzie, Sir Clifford Allbutt, and Sir William Osler. Dr Thomas Lewis was put in charge of the undertaking; and he, T F Cotton, and F H Thiele made a brief report on the problem in the *British Medical Journal* in November 1915.[10] Early in 1916 the Director-General of the Army Medical Service set aside the 250 bed Mount Vernon Hospital in Hampstead, London, for further investigation and rehabilitative treatment of the condition; late in 1917 the activities were transferred to a 700 bed hospital at Colchester in Essex. Other smaller rehabilitation centres were opened in other areas in 1918. British physicians assigned at the outset to Hampstead included John Parkinson, J C Meakins, and R M Wilson.

Six physicians from the United States (Samuel A Levine, Rufus A Morrison, Dr B S Oppenheimer, Marcus A Rothschild, William St Lawrence, and Frank N Wilson) who were experienced in cardiology were assigned in the summer of 1917 to Colchester by the Surgeon General of the United States Army on the advice of Dr Alfred E Cohn. Later, in 1918, the Surgeon General set aside 200 beds at the United States General Hospital No 9 at Lakewood, New Jersey, for the same purpose. These were under the direction of Dr Francis W Peabody. On 6 June 1918 the hospital was made a centre for cardiovascular disease. The medical officers there included Harry D Clough, Cyrus C Sturgis, and Joseph T Wearn.

One consequence of this heightened activity was a spate of new labels. Hartshorne had used the term "muscular exhaustion of the heart" in 1864, Da Costa had preferred "irritable heart" in 1871, Sir James Mackenzie used the label "general exhaustion" in 1916,[11] Thomas Lewis used "effort syndrome" in his 1919 monograph,[12] and the American workers preferred "neurocirculatory asthenia."[13] A vague wastebasket term, "disordered action of the heart", had also been used in the British Army, and the equally unsatisfactory term "soldier's heart" was used. In addition, the British army had the category "valvular disease of the heart", but in his series Lewis reported that 161 of 277 patients with this designation should be reclassified as "effort syndrome."[12]

The most active and the earliest interest in Da Costa's syndrome during this period came from British workers under Thomas Lewis who was the newest bright star in the cardiac firmament and a remarkable investigator.[14] Starting first at University College Hospital in London and then at the military hospitals in Hampstead and Colchester, Lewis and his team conducted a series of studies that resulted in more than 20 published papers.

Sir James Mackenzie who was a leading member of this group summarised his views of the syndrome as seen in British soldiers in a report published in the *British Medical Journal* in January 1916.[11] He found that a history of recent infections was present in most cases, and emphasised that fatigue and exhaustion were always present, and breathlessness was frequent. Depression and concern about heart disease was common, as were signs of vasomotor instability of the hands. In a 1920 article in the same journal, he wrote: "In a careful inquiry into the origin of ill health in over 2,000 soldiers I found that in the case of about 80 per cent, the first onset of their illness began with some complaint of an infectious nature... In a number of cases there was no history of infection, and the onset of the illness seemed to be due to a variety of circumstances... want of rest had evidently been the provoking agent in these instances."[15]

Another early publication from the group was that of Parkinson,[14] who described in 1916 his experience with 90 "cardiac" cases passing through a casualty clearing station in the British Expeditionary Force in France in the period March 1915 to January 1916.[16] He considered that 40 of these had "soldier's heart". Thirty nine of them complained of shortness of breath on exertion, 24 had precordial pain on effort (usually an ache that became sharper with increased exertion), 16 stated they were easily exhausted, and on auscultation nine had a short apical systolic murmur. After an average follow up of seven months, only nine were back on full duty and 17 were on light duty. He suggested that the "relative cardiac inefficiency" must represent the effects of previous infection, aging changes in men over 40, or a constitutional endowment of a heart "with limited efficiency".

A characteristic case cited was that of a 22 year old private. "Since age of 17, palpitation and shortness of breath on exertion. Light bench-work. September 1914, enlisted. Same symptoms on doubling or hurrying. September 1915 to France. Palpitation, shortness of breath, exhaustion and dull pain in fourth to sixth left spaces about nipple line, all on marching. After one month admitted. Examination: no abnormal physical findings. Eight months later: full duty in France but no better."

The group with Thomas Lewis reported other observations on these soldiers. Firstly, with test exercise they became more symptomatic than control subjects; they were able to do less physically than the controls, and their pulse rates and systolic pressures rose more than those of the presumed normal soldiers.[17] Second, there was no appreciable cardiac enlargement on orthodiographic measurement.[18] Third, they seemed to have a slightly reduced vital capacity.[19] Fourth, the men might show hyperalgesia in the precordial area.[20] Fifth, although in 1916 they reported that the "cause of breathlessness is absence of an adequate supply of buffer salts in the blood,"[21] a later (1919) study showed no clear reduction in the alkaline reserve of the blood.[22] Sixth, symptoms were not improved by the administration of digitalis.[23] Seventh, when given atropine, pilocarpine, and amyl nitrite they did not behave very differently from the control group.[24-26] Eighth, they did not develop distinctive changes in the PR intervals with and after effort.[27] Ninth, as described by Oppenheimer and Rothschild, they may have represented two populations—one with a positive family history and a history of symptoms before enlistment and one without such a background and with symptoms, particularly exhaustion and weakness, apparently precipitated by an event such as an acute infection.[28]

At Hampstead J C Meakins and R M Wilson examined the reaction of soldiers with this syndrome to a sudden visual stimulus followed by an "unexpected discharge of a blank cartridge under the examining couch".[29] Subjects exposed to this singular ordeal developed more rapid respiratory and pulse rates than did the normal soldiers. (It would not be surprising if other physiological and psychological effects resulted, but they were not described.)

In February 1918 in the *Lancet* Lewis pointed to the screening and rehabilitative value of a graded recreation and exercise programme conducted in the hospital.[30] Of 558 men discharged over a six month period in 1916 (average follow up of 11 months) approximately half could be returned to some duty capacity. Such a successful programme sounded remarkably easy to accept, especially for men coming from the trenches. Cohn described how the programme included "setting up exercises, marches with the band; there were round games and tennis, golf and cricket; athletic competitions, lectures and picture shows... There were theatricals, often arranged by the men themselves... And there was plenty of music; in one British camp there were two brass bands, an orchestra, a mandolin, and a banjo club."[7] Lewis proposed that a systematic course of exercise be made available in all large military hospitals, a recommendation strongly endorsed by Sir William Osler[31] and Sir James Mackenzie.[11]

Lewis summarised his experience in a 144 page monograph published in 1919 entitled "The soldier's heart and the effort syndrome".[12] He considered that such a rubric encompassed six subgroups—those with a constitutional nervous or physical weakness, some exposed to extraordinarily unfavourable conditions of work and sleep, those convalescent from acute infectious illnesses, a few with as yet unrecognised infection, a small group recovering from gas poisoning, and another small group with unrecognised heart disease. He considered it not remarkable that some men developed symptoms under wartime stresses, and pointed out that the syndrome was also found in civilian life. He emphasised the universality of the symptom breathlessness (only rarely found at rest), which he considered was probably related to acid-base alterations in the blood. Fatigue, he noted, was also universal as a complaint and half of the patients had vague left chest distress with or after effort, with at times hyperaesthesia of the skin or muscles of the chest wall. Palpitation was also very frequent, and there was occasional fainting and some giddiness. He did not agree with Hartshorne and Maclean that this syndrome represented heart strain. He did not find that consumption of alcohol or tobacco, or the presence of hyperthyroidism, were aetiological factors (patients with effort syndrome used less tobacco and alcohol than soldiers with gunshot wounds), nor did he find evidence for a primary defect of the nervous system. He concluded that the dominant aetiological factor in the clinical histories of soldiers complaining of the "effort syndrome" was "infection of one kind or another". In his emphasis on the role of infection, he agreed with Sir James Mackenzie. He encouraged the use of a hygienic regimen including outdoor activities, and of reassurance, and emphasised that bed rest was harmful.

After the armistice in 1918, Lewis assisted the British Ministry of Pensions in its assessment of cases of cardiovascular disability. An outpatient clinic was established at University College Hospital in London, and Parkinson was placed in charge of beds for convalescent cases at the Ministry of Pensions hospital at Orpington. (Brief summaries of the contributions of Lewis and his group during and immediately after the first world war may be found in the annual reports of the Medical Research Committee, 1914–1915 to 1919–1920, published in London by His Majesty's Stationery Office.)

In 1925 Dr Ronald T Grant, who was associated with Lewis, published a five year follow-up of 665 cases of "effort syndrome" seen at the Hampstead and Colchester Military Heart Hospitals during the years 1916–18 and who subsequently lived in the London area.[32] He traced over 90% of the men. Only 15% seemed to have recovered completely but the overall death rate in the group was not remarkable, although many of the men had developed pulmonary tuberculosis. He reasoned that incipient cardiac disease was not a factor in the syndrome.

Meanwhile, on the other side of the Atlantic in Lakewood, New Jersey, at the United States Army General Hospital No 9, a more modest wartime investigative effort was initiated. Dr Francis Peabody with Dr Clough, Dr Sturgis, Dr Wearn, and Dr Tompkins reported that 65 soldiers with the "constitutionally inferior" type of the syndrome showed an abnormal rise in systolic blood pressure or pulse rate or both in response to an intramuscular injection of adrenaline.[33] The same group without Peabody and Clough also administered an injection of atropine to these soldiers and noted that the rebound increase in pulse rate after an initial slowing was greater in the patients than in the control subjects.[34] Adams and Sturgis found little evidence of a reduced vital capacity in the men,[35] nor could they confirm the 1916 view of Lewis and his colleagues[21] of any abnormality in the carbon dioxide combining capacity of the blood and in acid-base balance.

A comprehensive report from the American side was prepared in 1919 by Dr Alfred Cohn of Rockefeller University, based both on his clinical experience in England at the Military Hospital at Colchester and in the hospitals of the American Expeditionary Force.[7] He reasoned that "the heart in convalescence after acute infectious disease and the Irritable Heart are probably not the same thing" and vigorously proposed that "this symptom complex is neurotic". He minimised but did not discard the importance of constitutional inferiority, writing that "taking constitutional predisposition into account is essential, but as a complete account of failure, it appears to be inadequate." He ended his paper with the conviction that "the disorder is essentially a neurosis, depending upon anxiety and fear; that it is removed by the disappearance of the inciting cause and that it is cured by measures designed to influence the neurotic state."

Neuhof, also writing in 1919 on the topic "The Irritable Heart in General Practice," believed that "the soldier's irritable heart is no new complex, but is the same syndrome seen in civil life, intensified and multiplied by training and war conditions."[36] He believed that "some great emotion, fright, dread, shock, is usually the directly antecedent cause of the outbreak of the cardiac symptoms. Reflex excitation from the gastrointestinal tract is the next most frequent." The fundamental process in his view was "hyperexcitation of the sympathetic nervous system".

Dr Paul Dudley White of Boston had received a letter from Dr Alfred Cohn dated 17 May 1917 suggesting that he become a member of the American contingent destined to go to England to work under Thomas Lewis at Hampstead and Colchester. Paul White, having been trained by Lewis, was clearly interested in the proposal but found that he, as a member of the United States Army Medical Corps Reserve, would not be released from his commitments to the Massachusetts General Base Hospital No 6. Indeed he was placed on active military service on 24 May 1917, only seven days after the date of Cohn's letter soliciting his participation. Paul White had visited the Hampstead Military Hospital on 29 August 1916 and was familiar with British interest in the subject.

Paul White's first publication in this area came after the war in 1920 when he pointed out that, since returning to civilian life, he had seen in six or eight weeks 12 young patients with "effort syndrome".[37] This was the first scientific paper to emphasise how common this problem was in civilian practice, and it was succeeded in 1934 by a more comprehensive discussion.[13] Most of his patients were women, their symptoms were typical, there was no evidence of organic heart disease, and he underscored the importance of correct diagnosis to avoid unnecessary invalidism. He did not support the views of Lewis and Mackenzie of an infectious or bacterial toxic aetiology for most cases. Here at last was an opportunity to consider the syndrome away from the unusual and often highly unfavourable conditions of wartime with their prevalence of respiratory and other infections, abnormal living conditions, uncertain diets, and fear of imminent death. Subsequently over the next 30 years he and his associates (especially Mandel E Cohen, and others including Edwin O Wheeler, Henry B Craig, William P Chapman, Stanley Cobb, Jacques Carlotti, and Eleanor W Reed) produced a series of reports that explored many facets of this puzzling condition. They used the term "neurocirculatory asthenia", which had been preferred by the United States investigators at the end of the first world war.

Cohen and White reported that 2–4% of the population had this disorder. The mean age of onset was about 25 years.[38] The disorder affected twice as many women as men, often occurring in successive generations in the same family. Unlike most earlier investigators they called attention to the chronic presence of sighing respirations, the complaint of smothering sensations (especially in crowds), and to the sign of a flushed face and neck; as well as to brisk patellar and Achilles deep tendon reflexes. In a 20 year follow up of 173 patients, over 70% continued to have some symptoms, but only 15% had important disability. Symptoms tended to increase with muscular effort, unusual emotion-provoking situations, disagreeable thoughts, and exposure to crowds, but two thirds of the patients could identify no stimulus. Painful stimuli such as heat and a tight sphygmomanometer cuff produced abnormal responses in subjects with neurocirculatory asthenia but not in controls. Patients could not continue as long as control subjects with moderate muscular effort, including running on a treadmill or stepping up and down. They also showed higher pulse and respiratory rates and blood lactate concentrations with exercise than the controls, and pulmonary ventilation was higher but oxygen consumption was the same. These observations coincided with those of the British workers Jones and Scarisbrick, published in 1946.[39] Rebreathing a mixture containing increased amounts of carbon dioxide often reproduced the symptoms. The symptoms of neurocirculatory asthenia were considered not to be identical with those of fear alone.

In 1958, Kannel *et al* reviewed the resting electrocardiogram of 203 individuals in the Framingham study considered to have neurocirculatory asthenia and concluded that no electrocardiographic abnormalities were characteristic of this syndrome,[40] a finding also reported by others.

Paul White and his group concluded that the cause of the condition was unknown and that simple reassurance and observation over time were the most effective therapeutic measures. In their last publication in 1972, Cohen and White additionally suggested that the syndrome might present in two forms—a mild disorder called neurocirculatory asthenia, and a severe illness that was actually manic depressive disease presenting at time with cardiovascular, respiratory, and fatigue symptoms in addition to other complaints.[41]

These extensive long term studies carried out under both peacetime and wartime (second world war) conditions in civilian and military populations give valuable information on many aspects of the problem. Most important of all, they drew attention to neurocirculatory asthenia in the daily practice of cardiology.

In the midst of these investigations by Paul White's laboratory, a major report on the syndrome was presented by Paul Wood in his three Goulstonian Lectures given to the Royal College of Physicians in London in 1941 during the second world war.[42] Paul Wood flatly stated that he no longer considered that the cause and mechanism were unknown. His was an extensive review of published reports with observations of his own. In his study of 200 military cases, the symptoms in order of frequency were breathlessness (93%), palpitation (89%), fatigue (88%), sweats (80%), nervousness (80%), dizziness (78%), and left chest pain (78%). Only 24% of the subjects could hold their breaths for 30 seconds or more, sweat was visible on the palms in 67%, and 48% appeared nervous. He considered that the left chest pain might have several explanations including a functional disturbance of the respiratory muscles, strain of the thoracic muscles, or "minimum trauma from the overacting heart of cardiac neurosis." He also commented on raised resting heart rates, sweating of the palms, soles, and axillae, and hyperventilation after forced breathing (but he did not believe that hyperventilation was responsible for the symptoms and signs). He considered that Da Costa's syndrome should be regarded "as an emotional reactive pattern peculiar to psychopathic personalities and to subjects of almost any form of psychoneurosis."

Paul Wood's conclusions included the following:

"The symptoms and signs of Da Costa's syndrome more closely resemble those of emotion, especially fear, than those of effort in the normal subject. The mechanism of somatic manifestations depends on central stimulation, not upon hypersensitivity of the peripheral autonomic 'gear'. This central stimulus is emotional, and is commonly the result of fear. The reaction becomes linked to effort by a variety of devices, which include misinterpretation of emotional symptoms, certain vicious circular patterns, the growth of a conviction that the heart is to blame, consequent fear of sudden death on exertion, conditioning and hysteria. Incapacity tends to be exaggerated consciously or subconsciously in order to protect the individual from further painful emotional experience."

Thus Paul Wood, after wartime experience with the condition, came down squarely on the side of viewing Da Costa's syndrome as a manifestation of emotion, more in keeping with the view of Cohn than that of Mackenzie or Lewis, and unlike that of White and Cohen, who considered that the issue was decidedly more complex.

It was doubtless in part because of Paul Wood's influential views, well spread over three issues of the *British Medical Journal* in 1941, that during the second world war there was a diminished interest in Da Costa's syndrome as a medical entity. Many of the cases seem to have been treated by psychiatrists and ended up with various diagnostic labels. In the third edition of his textbook on heart disease, published in 1968, Paul Wood restated his views in accord with this impression:

"It should be understood that there is no essential difference between 'effort syndrome' and 'cardiac neurosis', they are merely clothed differently, the former in battle dress, and latter in nylon. In civil life the condition accounts for 10 to 15 per cent of all cases referred to cardiovascular clinics; it is common in children, and occurs more often in women than in men, the ratio being 3:2. It has a preference for the emotional races, especially the Jews and Italians. In the first world war there were some 60,000 'effort syndrome' casualties in the British forces; in the second a more enlighted view was taken, the majority of these cases receiving appropriate psychiatric labels and management."[43]

Friedberg, in the third edition of his text *Diseases of the Heart,* published in 1966, also expressed a psychiatrically oriented view when he wrote: "The underlying cause appears to be a fundamental ego insecurity arising from psychological problems which began in infancy and childhood".[44] A more recent (1974) review by Caranasos expresses a similar sentiment.[45]

The past few years have seen two further lines of exploration. The first of these has been the suggestion by some that there is an overlap between neurocirculatory asthenia and mitral valve prolapse, and that both can be considered within a single rubric.

Jeresaty wrote in 1979 that "many of the patients previously described as suffering from Da Costa's syndrome, soldier's heart, the effort syndrome, and neurocirculatory asthenia would now be classified under the heading of mitral valve prolapse syndrome".[46] Barlow and Pocock stated in 1984: "We are also aware that some patients diagnosed by us as primary mitral valve prolapse syndrome would be classified by others as neurocirculatory asthenia, Da Costa's syndrome, non-specific T-wave changes, atypical chest pain syndrome, so-called 'syndrome X' or similar conditions".[47] It is important that Barlow and Pocock spoke only of "some patients". Wooley noted in 1985 and also earlier how "As knowledge and technology progressed, the pathway from neurocirculatory asthenia would eventually lead to anxiety neuroses of World War II, systolic click and late systolic murmur syndrome of the 1960's, and the mitral valve prolapse syndrome, panic disorders, and autonomic dysfunction states of the 1970's and 1980's".[48]

The fact that the disorders referred to all share uncertain aetiology, vague symptoms, no means of specific identification by laboratory means, and are usually unresponsive to conventional treatment should not in itself justify creating a new umbrella label. Because both mitral valve prolapse and neurocirculatory asthenia are common some individuals are likely to show evidence of both conditions.

It is important to emphasise, as have nearly all of those physicians who studied the problem carefully, that all patients with neurocirculatory asthenia complain of undue shortness of breath on effort and often at rest, approximately 90% have palpitation and fatigue, and approximately 50–75% report chest pain. This is not what has usually been reported with the mitral valve prolapse syndrome. It is apparent that most young patients with mitral valve prolapse syndrome have no symptoms at all if the condition is detected on a screening examination; and even among those seen in the usual clinic (office) setting, which concentrates those patients with symptoms, symptoms are much less common than in neurocirculatory asthenia. Jeresaty reported chest pain in 61%, fatigue in 42%, and dyspnoea in only 38% of 100 cases of mitral valve prolapse.[46] Barlow *et al* in their original 1968 description of 63 patients with systolic murmurs and in some cases non-ejection clicks, also described tiredness, palpitation, breathlessness, or chest pain in only 39 (62%).[49]

Leatham and Brigden wrote firmly in 1980 in an article entitled "Mild Mitral Regurgitation and the Mitral Prolapse Fiasco" that "*isolated* disease of the mitral valve causing mild or moderate reflux seldom causes symptoms other than those of iatrogenic anxiety."[50] Leor and Markiewicz from the Rambam Medical Center in Haifa, Israel, used auscultation and echocardiography to study 42 young soldiers with neurocirculatory asthenia; they concluded that "mitral prolapse and neurocirculatory asthenia do not appear to be related".[51] Silverman *et al* studied 68 patients seen in private practice, 57 of whom were women, in whom mitral valve prolapse was diagnosed by echocardiography.[52] While they concluded that the symptoms of neurocirculatory asthenia were more common in patients with mitral valve prolapse than in an age and sex matched control population, only 34 of the 68 complained of dyspnoea (as did 19 of the controls) and fatigue. Symptoms related to effort were not mentioned. Retchin *et al* investigated 274 outpatients and suggested that "symptoms and dysfunction are not related to the presence of mitral valve prolapse by echocardiography".[53] Devereux *et al* in another large study concluded that "non-anginal chest pain, dyspnoea, panic attacks and electrocardiographic abnormalities have appeared to be associated with mitral valve prolapse because of ascertainment bias and an erroneous classification of differences between men and women as being due to mitral valve prolapse".[54]

It seems best to keep neurocirculatory asthenia and mitral valve prolapse as separate categories for the time being because they do not have sufficient similarities to justify a single label. This does not mean that a few individuals do not demonstrate evidence of both conditions. The hyperkinetic heart syndrome also appears to be different from neurocirculatory asthenia and should also be considered as a separate entity.[55 56]

The second line of investigation has been the treatment of neurocirculatory asthenia with β blocking agents. Here, much as in the mitral valve prolapse story, there has been a modest amount of smoke but not much fire. Caranasos in 1974 summarised the situation as follows: "Recently propranolol has been found effective in diminishing or even abolishing the cardiovascular signs and symptoms of 'NCA', but the psychic symptoms are unaffected".[45] Rimon *et al* in an unimpressive, uncontrolled study published in 1979 in the *Israel Annals of Psychiatry*, listed many non-specific symptoms such as depression, palpitation, difficulty in falling asleep, tension headache, etc said to have been improved in 36 patients with neurocirculatory asthenia as result of treatment with propranolol.[57] No conclusions are justified from this evidence.

In 1974 Wolf *et al* of Hadassah University Hospital in Jerusalem treated five men and five women with neurocirculatory asthenia with intravenous propranolol. In all of them there was improvement in ST-T abnormalities in the resting electrocardiograms.[58] Here again, no definite conclusions can be drawn from such observations. Indeed, the whole area of the treatment of disorders associated with anxiety with β blocking drugs appears controversial.[59]

Da Costa's syndrome or neurocirculatory asthenia has been a common condition in the experience of many seasoned clinicians. Past studies have shown that it has often had a familial background, has occurred in both civilian and military life, and especially in women, has had certain identifiable symptoms, no specific signs, and few demonstrable physiological and psychological abnormalities. There has been no, or a poor, therapeutic response to rest, and no convincing evidence of benefit from diet, surgery (adrenal gland denervation was practised by Crile in the 1930s[60 61]), or drugs. A programme of reassurance, exercise, and physical fitness has been of value.

It is important to be able to recognise the condition irrespective of the label used. The diagnosis is usually not difficult for an interested reasonably intelligent physician. Be alert for the younger patient with unexplained shortness of breath, easy fatigue, and a history of palpitation and atypical chest pain, who sighs frequently during the course of the conversation. All too many patients with this syndrome, mainly women, are still mistakenly labelled as having organic heart disease including angina pectoris, and this leads to the additional problem of an unnecessary cardiac neurosis. (Not all patients with neurocirculatory asthenia have a cardiac neurosis and not all patients with a cardiac neurosis have neurocirculatory asthenia.) It is essential to be able to reassure the patient with neurocirculatory asthenia, to understand that the condition may be life long with remissions and exacerbations, and to appreciate that it may to some extent limit physically strenuous effort. Finally, it does not appear profitable at this time to attempt to combine neurocirculatory asthenia and mitral valve prolapse within a single diagnostic category.

References

1 Hartshorne H. On heart disease in the army. *Am J Med Sci* 1864;48:89–92.

2 Stillé A. *Address before the Philadelphia County Medical Society*. Philadelphia: Collins, Printer, 1863:18–19.

3 Maclean WC. Diseases of the heart in the British Army: the cause and the remedy. *Br Med J* 1867;i:161–4.

4 Da Costa JM. On irritable heart: a clinical study of a form of functional cardiac disorder and its con-

sequences. *Am J Med Sci* 1871;61(No. 121):17–52.

5 Wooley CF. Jacob Mendez Da Costa: medical teacher, clinician and clinical investigator. *Am J Cardiol* 1982;50:1145–8.

6 Howell JD. Soldier's heart: the redefinition of heart disease and specialty formation in early twentieth century Great Britain. *Med Hist* 1985;(suppl 5):34–52.

7 Cohn AE. The cardiac phase of the war neuroses. *Am J Med Sci* 1919;158:453–70.

8 Goldscheider A. Aufgaben und Probleme der inneren Medizin in Kriege Berliner. *Klin Wochenschr* 1915;52:1130–3, 1157–9.

9 Revue Analytique. *Arch Mal Coeur* 1916;9:355–65.

10 Cotton T, Lewis T, Thiele FH. A note on the "irritable heart" of soldiers. *Br Med J* 1915;ii:722.

11 Mackenzie J. The soldier's heart. *Br Med J* 1916;i:117–9.

12 Lewis T. *The soldier's heart and the effort syndrome.* New York: Paul B Hoeber, 1919:1–103.

13 Craig HR, White PD. Etiology and symptoms of neurocirculatory asthenia. *Arch Intern Med* 1934;53:645–8.

14 Pickering GW. In memoriam. *Clin Sci* 1948;6:3–11.

15 Mackenzie J. The soldier's heart and war neurosis. *Br Med J* 1920;i:491–4, 530–4.

16 Parkinson J. The cardiac disabilities of soldiers on active service. *Lancet* 1916;ii:133–8.

17 Cotton TF, Rapport DL, Lewis T. After effects of exercise on pulse rate and systolic blood pressure in cases of "irritable heart". *Heart* 1917;6:269–84.

18 Meakins JC, Gunson EB. Orthodiagraphic observations on the size of the heart in cases of so-called "irritable heart". *Heart* 1918;7:1–16.

19 Levine SA, Wilson FN. Observations on the vital capacity of the lungs in cases of "irritable heart." *Heart* 1919;7:53–61.

20 Meakins JC, Gunson EB. The occurrence of hyperalgesia in the "irritable heart of soldiers". *Heart* 1917;6:343–53.

21 Lewis T, Cotton TF, Barcroft J, *et al.* Breathlessness in soldiers suffering from irritable heart. *Br Med J* 1916;ii:517–9.

22 Wilson FN, Levine SA, Edgar AB. The bicarbonate concentration of the blood plasma in cases of "irritable heart." *Heart* 1919;7:62–4.

23 Parkinson J. Digitalis in soldiers with cardiac symptoms and a frequent pulse. *Heart* 1917;6:321–36.

24 Cotton TF, Rapport DL, Lewis T. Observation upon atropine. *Heart* 1917;6:293–8.

25 Cotton TF, Slade JG, Lewis T. Observations upon pilocarpine nitrate. *Heart* 1917;6:299–310.

26 Cotton TF, Slade JG, Lewis T. Observations upon amyl nitrite. *Heart* 1917;6:311–5.

27 Parkinson J, Drury AN. The P-R interval before and after exercise in cases of "soldier's heart". *Heart* 1917;6:337–42.

28 Oppenheimer BS, Rothschild MA. The psychoneurotic factor in the "irritable heart" of soldiers. *Br Med J* 1918;ii:29–31.

29 Meakins JC, Wilson RM. The effect of certain sensory stimulations on respiratory and heart rate in cases of so-called "irritable heart". *Heart* 1918;7:17–22.

30 Lewis T. Observations upon prognosis, with special reference to the condition described as the "irritable heart of soldiers." *Lancet* 1918;i:181–3.

31 Osler W. Graduated exercise in prognosis. [Letter]. *Lancet* 1918;1:231.

32 Grant RT. Observations on the after-histories of men suffering from the effort syndrome. *Heart* 1925;12:121–42.

33 Peabody FW, Clough HD, Sturgis CC, Wearn JT, Tompkins EH. Effects of the injection of epinephrin in soldiers with "irritable heart." *JAMA* 1918;71:1912–3.

34 Sturgis CC, Wearn JT, Tompkins EH. Effects of the injection of atropin on the pulse-rate, blood-pressure and basal metabolism in cases of "effort syndrome." *Am J Med Sci* 1919;158:496–502.

35 Adams FD, Sturgis CC. Note on the vital capacity of the lungs and the carbon dioxide combining capacity of the blood in cases of "effort syndrome." *Am J Med Sci* 1919;158:816–8.

36 Neuhof S. The irritable heart in general practice. *Arch Intern Med* 1919;24:51–64.

37 White PD. The diagnosis of heart disease in young people. *JAMA* 1920;74:580–2.

38 Cohen ME, White PD. Life situations, emotions, and neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome). *Psychosom Med* 1951;13:335–57.

39 Jones M, Scarisbrick R. Effect of exercise on soldiers with neurocirculatory asthenia. *Psychosom Med* 1946;8:188–92.

40 Kannel WB, Dawber TR, Cohen ME. The electrocardiogram in neurocirculatory asthenia (anxiety neurosis or neurasthenia): a study of 203 neurocirculatory asthenia patients and 757 healthy controls in the Framingham study. *Ann Intern Med* 1958;49:1351–60.

41 Cohen ME, White PD. Neurocirculatory asthenia: 1972 concept. *Milit Med* 1972;137:142–4.

42 Wood P. Da Costa's syndrome (or effort syndrome). *Br Med J* 1941;i:767–72, 805–11, 845–51.

43 Wood P. *Diseases of the heart and circulation.* 3rd ed. London: Eyre and Spottiswoode, 1968:1074–5.

44 Friedberg CK. *Diseases of the heart.* 3rd ed. Philadelphia: WB Saunders, 1966:1721.

45 Caranasos GJ. Neurocirculatory asthenia. In: Eliot RS, ed. *Stress and the heart.* Mt Kisco, New York: Futura, 1974:235–8.

46 Jeresaty RM. *Mitral valve prolapse.* New York: Raven Press, 1979:44.

47 Barlow JB, Pocock WA. The mitral valve prolapse enigma—two decades later. *Mod Concepts Cardiovasc Dis* 1984;53:13–7.

48 Wooley CF. From irritable heart to mitral valve prolapse: British Army medical reports, 1860 to 1870. *Am J Cardiol* 1985;55:1107–9.

49 Barlow JB, Bosman CK, Pocock WA, Marchand P. Late systolic murmurs and non-ejection ("mid-late") systolic clicks. An analysis of 90 patients. *Br Heart J* 1968;30:203–18.

50 Leatham A, Brigden W. Mild mitral regurgitation and

the mitral prolapse fiasco. *Am Heart J* 1980;**99**:659–64.

51 Leor R, Markiewicz W. Neurocirculatory asthenia and mitral valve prolapse—two unrelated entities? *Isr J Med Sci* 1981;**17**:1137–9.

52 Silverman BD, Berry JN, Flowers C. Mitral valve prolapse: its symptom complex and its association with Da Costa's syndrome. *South Med J* 1984;77:27–9.

53 Retchin SM, Fletcher RH, Earp J, Lamson N, Waugh RA. Mitral valve prolapse. Disease or illness. *Arch Intern Med* 1986;**146**:1081–4.

54 Devereux RB, Kramer-Fox R, Brown WT, *et al.* Relation between clinical features of the mitral valve prolapse syndrome and echocardiographically documented mitral valve prolapse. *J Am Coll Cardiol* 1986;**8**:763–72.

55 Gorlin R. The hyperkinetic heart syndrome. *JAMA* 1962;**182**:823–9.

56 Gillum RF, Teicholz LE, Herman MV, Gorlin R. The idiopathic hyperkinetic heart syndrome: clinical course and long-term prognosis. *Am Heart J* 1981;**102**:728–34.

57 Rimon R, Kampman R, Viukari M. Propranolol in the treatment of neurocirculatory asthenia—an open pilot study. *Isr Ann Psychiatry* 1979;**17**:144–8.

58 Wolf E, Braun K, Stern S. Effects of beta-receptor blocking agents propranolol and practolol on ST-T changes in neurocirculatory asthenia *Br Heart J* 1974;**36**:872–9.

59 Hollister LE. *Clinical pharmacology of psychotherapeutic drugs*. New York: Churchill Livingstone, 1983:38.

60 Crile GW. Recurrent hyperthyroidism, neurocirculatory asthenia and peptic ulcer. *JAMA* 1931;**97**:1616–8.

61 Crile G. Denervation of the adrenal glands for neurocirculatory asthenia. *Surg Gynecol Obstet* 1932;**54**:294–8.

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Blood flow patterns in the human aorta studied by magnetic resonance

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SUMMARY Magnetic resonance velocity mapping by the field even echo rephasing sequence was used to provide two dimensional velocity profiles in the ascending and the descending aorta. Flow patterns were studied in ten healthy volunteers by a display method that gave clear details of the profiles. Velocity profiles in the ascending aorta were skewed in systole with an axis of skew roughly symmetrical about the plane of the aortic arch. During diastole flow was reversed along the posterior left wall of the ascending aorta while it continued forwards at the anterior right wall. In the descending aorta plug flow occurred but with minimal skew. Flow along the right wall was reversed during diastole. Turbulent flow did not occur in the ascending or descending aorta of any healthy subject.

Magnetic resonance velocity mapping is a very powerful tool for the study of cardiovascular physiology. Its non-invasiveness, its quantitative two-dimensional data, its accuracy, and its high spatial resolution make it suitable for clinical use.

The complex phenomena of blood flow in the heart and blood vessels are worthy of study because they give an insight into the normal and pathological function of the cardiovascular system. Flow profiles are known to be modified in some diseases[1 2] and are of crucial importance in others (for example steal syndromes). Our current knowledge of velocity profiles in the great vessels has come from invasive techniques such as catheter injection of oil droplets,[3] and the hot-film anemometer,[4 5] or from non-invasive ones such as the pulsed Doppler flow meter[1 2 6] whose access to some blood vessels may be limited.

The recent advent of magnetic resonance velocity mapping[7 8] using the field even echo rephasing sequence[9–11] has made it possible to obtain accurate velocity profiles in two dimensions at any point in the cardiac cycle. The technique is entirely non-invasive making it ideal for the study of flow patterns in vivo.

We report the analysis of aortic flow patterns in the ascending and descending aorta of 10 healthy volunteers.

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Principles of magnetic resonance velocity mapping

The principles of the magnetic resonance phenomenon and the methods whereby these properties may be translated into non-invasive images are amply reviewed by Pykett *et al.*[12] We will confine our description to those principles necessary to the understanding of how a parametric image of velocity may be produced. Although the phenomena follow the laws of quantum mechanics the quantum mechanical behaviour of populations of nuclei can accurately be described along the more readily comprehensible classical lines given below.

The hydrogen nucleus gives rise to the magnetic resonance signals used in clinical images. Nuclei spin on their axes, and in a magnetic field these axes of spin precess about the direction of the applied magnetic field (fig 1). The frequency of precession is directly proportional to the magnetic field that each nucleus experiences. The nuclei may be excited by the application of a radiofrequency pulse perpendicularly to the field and at the frequency of precession. This changes the angle (but not the axis) of precession by an amount depending on the strength and duration of the radiofrequency pulse. As the nuclei return to equilibrium they emit radio signals at the frequency of precession which can be detected in a

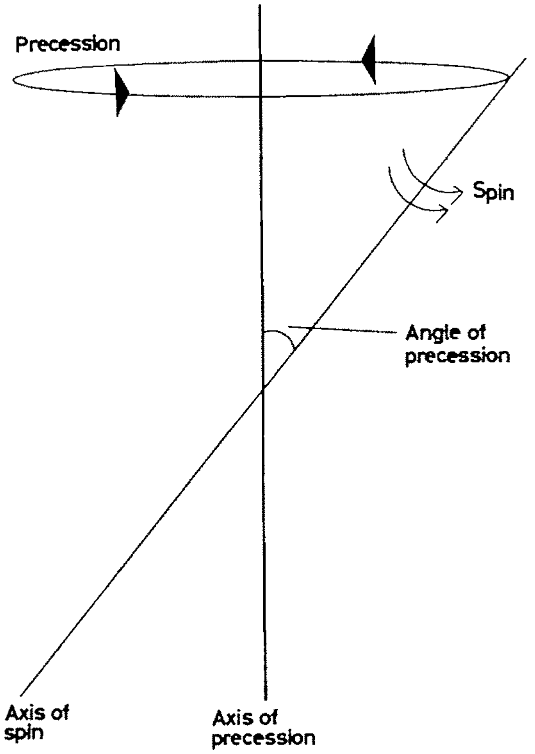

Fig 1 *Definition of terms for the concepts of nuclear spin and precession of the axis of spin.*

radio aerial and processed by a computer to produce the image.

The strength of the radio signal received at any time depends on the number of nuclei in phase. If the precessions are uniformly distributed around the circumference of the circle shown in fig 1, no radio signal can be detected because those nuclei pointing in one direction have their signal cancelled by those diametrically opposite. If the precessions have a single phase, so that all point in one direction, a large radio signal is detectable.

The geometry of excitation with the radiofrequency pulse brings the nuclei into partial phase (for the hydrogen nucleus the nuclei occupy a little less than one third of the circumference of the circle). The radio signal decays away for several reasons; in the context of velocity mapping the most important of these is the loss of the phase coherence obtained during excitation.

The phase loss occurs because the magnetic field experienced by each nucleus is slightly different, either owing to its different chemical environment or to non-uniformities of the magnetic field or both. Because precession frequency is proportional to the field experienced by the nucleus, a range of precession frequencies is generated. As some nuclei precess more slowly and others more quickly their phase spreads around the circle.

Loss of phase can also be produced artificially by deliberately subjecting the sample to a non-uniform magnetic field. If the non-uniformity is generated by a gradient varying linearly from one side of the body to the other then phase will vary according to the position of the nucleus in space along the gradient. This property is used to generate the spatial resolution, which in conjunction with computerised image reconstruction methods[13-15] produces images.

If phase has been disturbed by applying a gradient for a time, it may be restored by applying an equal and opposite gradient for an identical length of time. Nuclei whose precession was speeded up are now slowed down and vice versa. The precession of the nuclei returns to phase coherence, a phenomenon known as gradient refocusing.

The equations used by the image reconstruction method of two dimensional Fourier transformation[15] may be solved for the phase of the nuclei in any voxel. In magnetic resonance studies a slice of finite thickness is imaged, so that the image element has a height equal to the slice thickness and cross section equal to the pixel area. This three dimensional image element is called a voxel. An image in which each voxel has the value of the average phase within it is called a phase image.

We can encode velocity as phase by superimposing gradients on those used for imaging. If a gradient is put on in the direction in which velocity is to be measured (either perpendicular to the slice or in any direction within it), the nuclei in each voxel will receive a phase signature. If an equal and opposite gradient is then put on in this direction this phase signature will be lost by cancellation of the phase disturbance imposed by the first gradient.

Cancellation will only occur if the nucleus remains in the same place in the gradient. If it is moving up the gradient, its first phase signature will be more than cancelled by the second, since by the time the second is applied the nuclei are experiencing a stronger magnetic field. A negative phase will result. If it is moving down the gradient a positive phase will result. This resultant phase will be proportional to the velocity component in the direction of the gradient.

For very high velocities, the over or under cancellation may be so great that the resultant phase differs by more than one revolution. Because phase is an angle, it may only uniquely lie within the range of a single revolution. Two velocities, one producing a given phase angle and the other a phase angle equal to one or more revolutions plus the first are interpreted as being identical. The size and duration of the velocity encoding gradients and the time between them are thus chosen so that the maximum velocity encountered will give a phase angle which is less than one complete revolution. Since with bidirectional flow it is often necessary to consider high velocities in both directions, the maximum in one direction must not exceed half a revolution. (If it is known before acquisition that maximum forward velocity will be larger than maximum reverse velocity, the gradients can be tailored so that the sum of phase angles from the maximum forward and reverse velocities is one complete revolution.)

In practice, inhomogeneities of the main magnetic field produce artefacts on the phase map. This problem is overcome by acquiring two images, one with velocity encoding gradients and the other without, and subtracting the two phase maps.

A further refinement is necessary before velocity mapping is practical in large vessels. Where accelerations are large, a voxel will contain a wide range of different velocities, and therefore a large number of resultant phases after the flow encoding sequence. Because these are out of phase with each other there is signal loss. This problem is overcome by even echo rephasing which refocuses the range of phases in a manner similar to gradient refocusing.[9] Even so, gross turbulence within a voxel will still result in signal loss.

Patients and methods

A Picker International Vista 2055 magnetic resonance machine, operating at 0·5 T was used. Ten healthy volunteers without a history of cardiac disease were studied after they had given informed consent. Electrocardiographically gated velocity maps were obtained in the transverse plane by the field even echo rephasing sequence with gradient modification to encode velocity in the phase of the magnetic resonance signal (see principles of magnetic resonance velocity mapping above). To compensate for inhomogeneities of the magnetic field, a reference image without gradient modification was subtracted from the one with modification. Up to 12 frames (depending on heart rate) were obtained at a level at which the ascending aorta was perpendicular to the transverse plane—that is the level of the right pulmonary artery. Views of both the ascending and the descending aorta were thus obtained in a single transverse section. The first frame corresponded to a point in the cycle 20 ms after the onset of the electrocardiographic R wave; frames were obtained at 50 ms intervals.

A 128 × 128 pixel image was sampled twice (improving the signal to noise ratio). Acquisition thus took about five minutes depending on heart rate. The field of view was 45 cm but the image was interpolated in two dimensions during reconstruction, giving a voxel dimension of 1·8 × 1·8 × 10 mm. Two dimensional Fourier transformation in which the magnitude and phase were calculated for each pixel was used as the method of image reconstruction. Masking of the phase reconstruction to show zero veolocity in pixels with a magnitude value of less than 10% of maximum reduced the random phase values caused by background noise.

After acquisition, the velocity maps were transferred to an off line computer system (Sperry Univac V77–600) for further processing. A window of 32 × 32 pixels was selected and positioned such that the ascending aorta appeared centrally in the 220 ms frame. This window position was used for all images in the cycle, thus ensuring accurate registration of frames for cine display. These images were scaled so grey levels corresponded exactly on all of them. They were then stored and displayed with a coarse grey scale of 12 levels to produce a pseudocontouring effect.[16] An identical process was used for descending aortic windows over the same velocity maps.

Results

Figure 2 shows a series of contoured velocity profiles at the indicated points of the cardiac cycle in the ascending aorta of a typical subject. Mid-grey signifies no flow, black flow out of the image plane, and white flow into the image plane. All the subjects studied showed qualitatively identical patterns throughout the cycle with the exception of one in whom the only difference was a peak diastolic reverse flow which was rotated towards the left side of the aorta by 90°.

Ascending aortic flow maps showed the following features: (*a*) plug flow occurred during most of systole. (Plug flow is the smooth flow of an inviscid fluid with a velocity profile which is uniform across the vessel. Instead of flow being slow near the edges of the pipe and rapid in the middle, a quasi-solid "plug" of fluid moves down the pipe.) The velocity profile was skewed towards the posterior left wall of the vessel; (*b*) during diastole, flow continued rapidly forward at the anterior right wall while simultaneously moving rapidly backwards at the posterior left wall; (*c*) flow never became turbulent. In fig 3 the data of fig 2 are redisplayed as a perspective three dimensional plot. This eases interpretation, but it requires considerable image processing. The spatial localisation of peak velocities (mean (SD)) in the

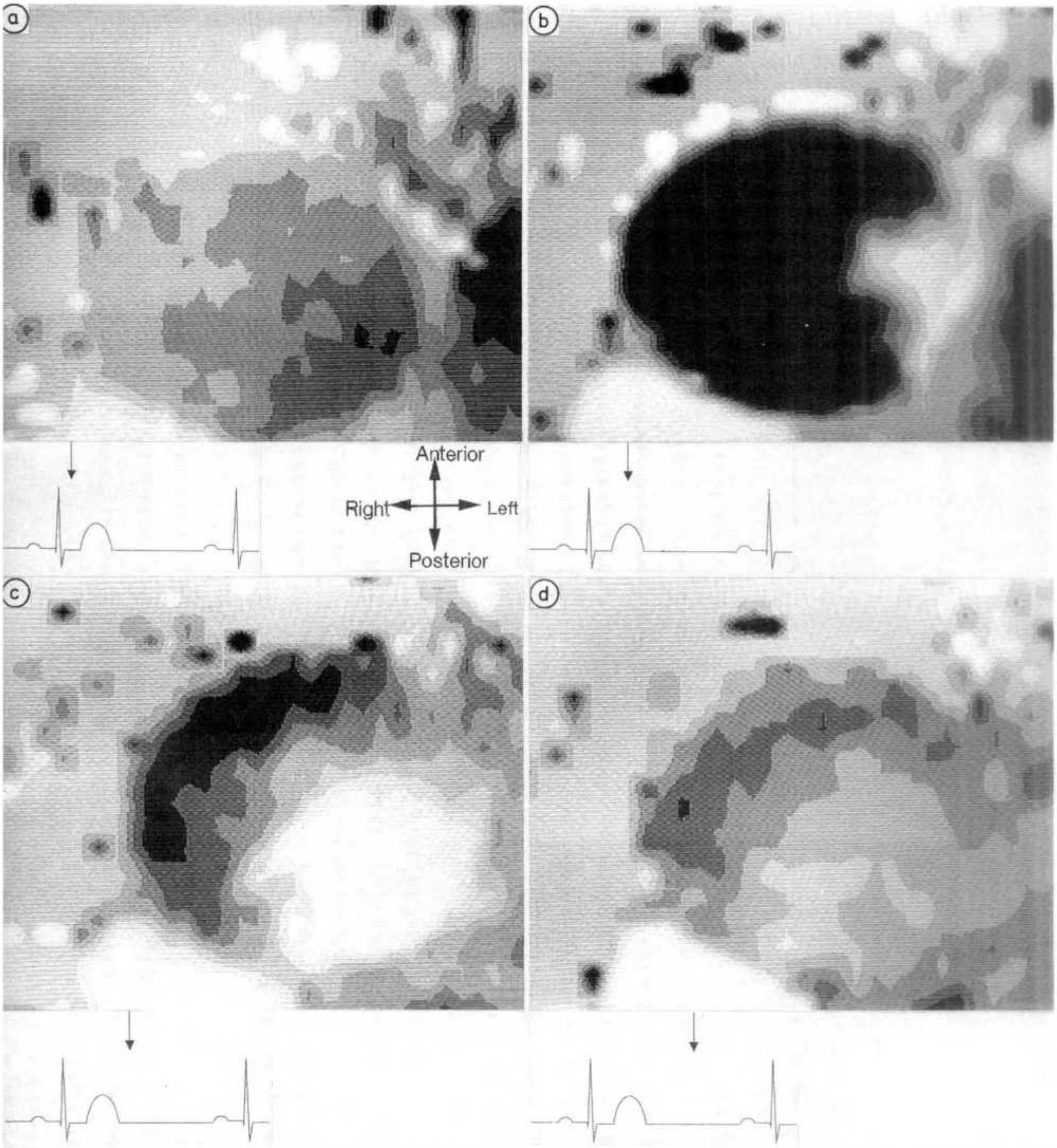

Fig 2 *A series of pseudocontoured velocity maps of the ascending aorta in a healthy volunteer. Each grey level corresponds to a range of flow velocities. Mid-grey signifies no flow, black flow out of the image plane, and white flow into the image plane. The times for each frame are indicated by the accompanying electrocardiogram trace, and the orientation is as shown. Note the skewing of the velocity during rapid ejection (a), the start of flow reversal (b) at 220 ms (well before aortic valve closure), the dominance of the reverse flow channel while forward flow continues at the anterolateral wall at 370 ms (c), and the cessation of reverse flow at 570 ms (d). Note that all the velocities in (d) are either zero or in the forward direction.*

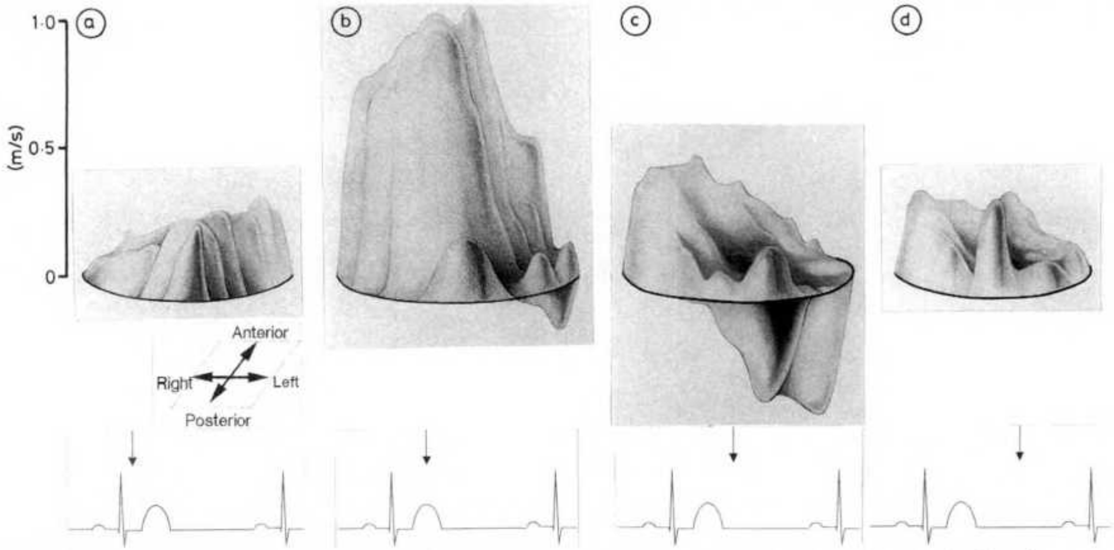

Fig 3 *Two-dimensional velocity profiles shown in fig 2 redisplayed as three-dimensional surfaces. Velocity is plotted vertically to the indicated scale.*

ascending aorta in the ten subjects was 129° (14) for the systolic forward flow axis −89° (20) for the diastolic forward flow axis, and 122° (15) for the diastolic reverse flow axis.

The descending aortic flow maps were broadly similar to those of the ascending aorta. The important differences were that: (*a*) plug flow occurred, but the velocity profile has lost its skewness at this level; (*b*) flow reversed at the right wall of the vessel during diastole in all but two subjects.

Discussion

The ability to study two-dimensional velocity profiles non-invasively makes it possible to study complex flow phenomena without the disturbances that may be induced by more invasive methods.

FLOW PATTERNS

All the subjects showed qualitatively identical flow patterns in systole. There was also excellent correspondence of flow patterns in diastole, with a single exception. In this one case diastolic reverse flow occurred anteriorly rather than posteriorly towards the left wall of the ascending aorta.

Ascending aortic blood shows both forward and reverse flow during diastole. The total reverse flow is too great for all of it to pass into the coronary ostia; rather it seems that a circulation is set up around the sinus of Valsalva, with a proportion of the recirculating blood flowing into the coronary arteries. At the imaged level in the descending aorta there is a little reverse flow when the pressure upstream falls. In two subjects, reverse flow in the descending aorta was not seen, implying that the leading edge of the recirculating flow occurred near the imaged plane (that is high in the descending aorta).

The skewness of the velocity profile and its axis of symmetry (which lies in the plane of the aortic arch) has implications for the accuracy of aortic blood flow as calculated by range gated Doppler ultrasound. Skewness makes methods of interpreting flow at a single point in the aorta as mean flow vulnerable to error. Weighted average methods assuming semicircular symmetry for velocities obtained along an axis[1 6] will depend critically on the choice of that axis. Since the axis and velocity peaks do not remain stationary within the aorta, the errors in flow estimates will vary with the point in the cardiac cycle.

The reverse flow occurring during late systole and throughout most of diastole can also affect the echocardiographic findings. If the ultrasound beam is directed to detect flow near the posteromedial aortic wall, abnormally short ejection phases can be found[17] and the estimates of flow will be inaccurate.

All the above features of ascending and descending aortic velocity profiles accord with those found in animals by invasive methods, such as oil droplet injection,[3] and hot-film anemometry,[4 5 18] and with ultrasound findings.[19] They also accord with ultrasound work in man.[1 2 6] The restriction of axes to anteroposterior and right-left in some anemometer[4] and ultrasound[19] work masks the true axis of skew as revealed by the two-dimensional magnetic resonance velocity maps.

The flow patterns obtained resemble those obtained by Paulsen and Hasenkam in the ascending aorta in dogs 5 cm above the aortic valve.[5] They showed that the two-dimensional velocity profiles changed considerably from a level 2 cm above the valve to a level 5 cm above it. Thus when studies are compared the levels must correspond. The reference plane in this study is that of the right pulmonary artery, which is a little more than 5 cm from the centre of the aortic valve.[20]

The phenomena occurring as blood is ejected into the aorta are complex. The viscous properties of blood, the pulsatility of the flow, the elasticity of the aorta, the propagation and reflection of the shock waves generated during ventricular contraction, the entrance region effects, and flow into vessels arising from the aorta must all be taken into account[21] when theories are proposed to account for the observed phenomena.

One consistent finding in this and the other studies[22] has been skewing of the systolic velocity profile towards the posterior wall of the ascending aorta during systole. The velocities are fastest where the radius of curvature is least. This finding disagrees with the theoretical predictions of McDonald.[23] Seed and Wood have provided a simple model of flow of an inviscid fluid in a curved pipe,[4] which suggests that velocities are inversely proportional to the radius of curvature—that is faster velocities occur near the wall on the inside of the curve. In our study the gradient of the systolic profile reached a maximum in the plane of the aortic arch, which is consistent with the theory of Seed and Wood.

In these normal subjects, there was no turbulent flow. Anything more than minimal turbulence would show as signal loss not correctable by even echo rephasing. Some have reported turbulence,[5 24] particularly when anemometry has been used in smaller animals, or they have surmised that it occurs.[25] This may be because the presence of the anemometer probe in the aortic lumen disturbs flow that is already at the limits of its stability as non-turbulent flow. Some have commented on signs of instability or streamlines stopping short of fully developed turbulence because of the short duration of very rapid flow.[5]

Simultaneous forward and reverse flow can occur in a single channel in a vessel without causing turbulence, provided that the shearing forces are not too great and no other generator of turbulence, such as a stenotic valve, is present. This may be appreciated by considering ripples on the surface of water. At any instant there are peaks and troughs. If a velocity map were to be acquired in the plane of the surface of the water, recording velocities into and out of the plane, there would be some areas of upward velocity and adjacent areas of downward velocity, bounded by lines of zero velocity. Turbulent flow is not occurring in these ripples even though bidirectional flow would be seen on the velocity map.

MAGNETIC RESONANCE VELOCITY MAPPING

Magnetic resonance velocity mapping has great advantages over other methods for the study of flow patterns. Oil droplet injection and hot film anemometry are invasive and time-consuming. They are not suited to routine clinical use. By use of a special mounting apparatus,[5] hot film anemometry can be adapted to the measurement of two-dimensional velocity profiles in animals. Its technical limitations make it unsuitable for the study of the boundary layer.

Pulsed Doppler echocardiography can be used to provide velocity profiles in large vessels in both animals and in man. It has the advantage of being non-invasive, but its velocity profiles must be one-dimensional if a sufficient number of velocity levels are to be resolved. It is possible to obtain two-dimensional echocardiographic velocity profiles[26] but with only a few steps of velocity,[27] which is insufficient for the generation of enough flow contour levels. Pulsed Doppler methods also suffer from aliasing at high velocities.[28] Movement of the aortic wall into and out of the sample volume makes it very difficult to study the boundary layer, though tracking methods may partially eliminate artefact from this cause.

Magnetic resonance velocity mapping has the advantages of being non-invasive, intrinsically two-dimensional, and has very high resolution of velocity. Comparisons of cardiac output derived from chamber volume estimates[29] and those measured by summation of aortic velocities in all frames show agreement to within 7%. The use of the field even echo rephasing sequence to avoid signal loss permits its use in both the ascending and the descending aorta as well as in other vessels of clinical importance. Up to 12 frames per cycle may be produced in short acquisition times and access to some vessels is not limited as it is with echocardiography. Because it does not depend on range gating, it is not limited by movement of the aortic wall from frame to frame, making it suitable in principle for the study of the boundary layer.

Although the present study used a resolution (before interpolation) giving a pixel size greater than the size of the boundary layer, higher resolution is not difficult to achieve. The close-packed contours of fig 2 confirm what has been suspected from hot film anemometry—that is that the boundary layer is thin (1–2 mm), and that shear rates in it are extremely high.

Velocity mapping is suitable for use in small vessels where the lower accelerations make velocity easier to measure. Maps have been obtained in carotid arteries, vertebral arteries, and jugular veins,[7] and in femoral arteries and veins.[30]

DISPLAY SYSTEM

The use of a pseudocontoured display[16] has advantages over the use of contour lines, especially when cine displays are used. This is because the effect of having far fewer grey scale levels than pixel values forces whole ranges of pixel values to be displayed as a single shade of grey. Each shade of grey thus signifies a specific velocity range.

The use of a restricted number of grey levels does not overload the visual system, thereby simplifying interpretation. By adjustment of window width and level (analogous to contrast and brightness), the contours can be made to move over the velocity profile giving considerable information about its three-dimensional structure. With training it is possible to visualise this structure very clearly and quickly.

As well as its information content, this type of display does not require image processing. It is produced very simply and rapidly by switching the display monitor to a coarse grey scale. While the quasi-three-dimensional displays of fig 3 may be easier to comprehend without training, their routine production requires considerable computing power and time.

Conclusion

Magnetic resonance velocity mapping is a non-invasive method that provides accurate two-dimensional velocity maps anywhere in the cardiovascular system. Its application to the ascending and descending aorta clearly defines consistent normal flow patterns and the non-turbulent nature of the flow. Its application to the study of the boundary layer, and to the modification of flow patterns in the presence of atheroma in smaller vessels will be of help both in diagnosis and in contributing to our understanding of the pathophysiology of cardiovascular disease.

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References

1 Jenni R, Vieli A, Anliker M, Krayenbuehl HP. Doppler-echocardiography: its advantages and limitations in adult cardiology. In: Roelandt D, ed. *The practice of M-mode and two dimensional echocardiography* The Hague: Martinus Nijhoff, 1983;90–7.

2 Jenni R, Ruffman K, Vieli A, Anliker M, Krayenbuehl HP. Dynamics of aortic flow in hypertrophic cardiomyopathy. *Eur Heart J* 1985;6:391–8.

3 Ohlsson NM. Left heart and aortic flow patterns in the dog. Precision motion analysis of high speed (270 frames/sec.) cinefluorographic recordings. *Acta Radiol* 1962;suppl 213:1–80.

4 Seed WA, Wood NB. Velocity patterns in the aorta. *Cardiovasc Res* 1971;5:319–30.

5 Paulsen PK, Hasenkam JM. Three-dimensional visualisation of velocity profiles in the ascending aorta in dogs measured with a hot film anemometer. *J Biomechan* 1983;16:201–10.

6 Jenni R, Vieli A, Ruffman K, Krayenbuehl HP. A comparison between single gate and multigate ultrasonic Doppler measurements for the assessment of the velocity pattern in the human ascending aorta. *Eur Heart J* 1984;5:948–53.

7 Bryant DJ, Payne JA, Firmin DN, Longmore DB. Measurement of flow with NMR imaging using a gradient pulse and phase difference technique. *J Comput Assist Tomogr* 1984;8:588–93.

8 Underwood SR, Firmin DN, Klipstein RH, Rees RSO, Longmore DB. Magnetic resonance velocity mapping: clinical application of a new technique. *Br Heart J* 1987;57:404–12

9 Pattany PM, Nayler GL. High velocity flow imaging by even echo rephasing. Society of Magnetic Resonance in Medicine, Fourth Annual Meeting, London, 1985. Book of Abstracts, 599–600. Berkeley, California: Society of Magnetic Resonance in Medicine.

10 Longmore DB, Firmin DN, Nayler GL, Underwood SR, Klipstein RH. Cine magnetic resonance blood flow imaging in clinical use [Abstract]. *Mag Reson Imaging* 1986;4:157.

11 Nayler GL, Firmin DN, Longmore DB. Blood flow imaging by cine magnetic resonance. *J Comput Assist Tomogr* 1986;10:715–22.

12 Pykett IL, Newhouse JH, Buonanno FD, *et al.* Principles of nuclear magnetic resonance imaging. *Radiology* 1982;143:157–68.

13 Hounsfield GN. Computerised transverse axial scanning (tomography), Part I. Description of system. *Br J Radiol* 1973;46:1016–22.

14 Lauterbur PC. Image formation by induced local interactions. Examples employing nuclear magnetic resonance. *Nature* 1973;242:190–1.

15 Kumar A, Welti D, Ernst R. NMR Fourier zeugmatography. *J Magn Reson* 1975;18:69–83.

16 Delp EJ, Buds AJ. Digital image processing. In: Buda AJ, Delp EJ, eds. *Digital cardiac imaging.* Dordrecht: Martinus Nijhoff, 1985:5–23.

17 Louie EK, Maron BJ, Green KJ. Variations in flow-velocity waveforms obtained by pulsed Doppler

echocardiography in the normal human aorta. *Am J Cardiol* 1986;58:821–6.

18 Freis ED, Heath WC. Hydrodynamics of aortic blood flow. *Circ Res* 1964;14:105–16.

19 Peronneau P, Sandman W, Xhaard M. Blood flow patterns in large arteries. *Ultrasound in Medicine* 1977;38:1193–208.

20 Gray H. *Gray's anatomy*. 35th ed. Warwick R, Williams PL, eds. London: Longman, 1973:617.

21 McDonald DA. *Blood flow in arteries*. 2nd ed. London: Edward Arnold, 1974.

22 Caro CG, Pedley TJ, Schroter RC, Seed WA. *The mechanics of the circulation*. Oxford: Oxford University Press, 1978:316–7.

23 McDonald DA. *Blood flow in arteries*. 2nd ed. London: Edward Arnold, 1974:90.

24 McDonald DA. *Blood flow in arteries*. 2nd ed. London: Edward Arnold, 1974:80.

25 Caro CG, Pedley TJ, Schroter RC, Seed WA. *The mechanics of the circulation*. Oxford: Oxford University Press, 1978:332–3.

26 Miyatake K, Mitsunori O, Kinoshita N, *et al*. Clinical applications of a new type of real-time two dimensional Doppler flow imaging system. *Am J Cardiol* 1984;54:857–68.

27 Miyatake K, Izumi S, Shimizu A, *et al*. Right atrial flow topography in healthy subjects studied with real-time two dimensional Doppler flow imaging technique. *J Am Coll Cardiol* 1986;7:425–31.

28 Snider AR. Doppler echocardiography: basic principles and clinical applications. In: Buda AJ, Delp EJ, eds. *Digital cardiac imaging*. Dordrecht: Martinus Nijhoff, 1985:182–206.

29 Longmore DB, Klipstein RH, Underwood SR, *et al*. Dimensional accuracy of magnetic resonance studies of the heart. *Lancet* 1985;i:1360–2.

30 Underwood SR, Firmin DN, Klipstein RH, Rees RSO, Longmore DB. Magnetic resonance velocity mapping:clinical application of a new technique. *Br Heart J* 1987;57:404–12.

Br Heart J 1987;58:324–32

Value of the resting 12 lead electrocardiogram and vectorcardiogram for locating the accessory pathway in patients with the Wolff-Parkinson-White syndrome

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SUMMARY The resting 12 lead electrocardiogram and vectorcardiogram were reviewed in 47 patients with the Wolff-Parkinson-White syndrome (*a*) who had pre-excitation on the resting 12 lead electrocardiogram, (*b*) who had a single anterograde conducting accessory pathway assessed and located during preoperative electrophysiological study and during epicardial mapping at operation, and (*c*) in whom surgical division of the accessory pathway resulted in loss of pre-excitation. The site of the accessory pathway established during operation was compared with that established by evaluating the polarity of the delta wave and QRS complex on the resting 12 lead electrocardiogram. The electrocardiogram was assessed by the Rosenbaum criteria (Wolff-Parkinson-White type A, left-sided pathway; or type B, right-sided pathway), the Gallagher criteria (atrial pacing resulting in maximal pre-excitation), and the World Health Organisation criteria (a composite of previous studies). The Gallagher and World Health Organisation criteria were derived from patients demonstrating maximal pre-excitation that often required atrial pacing. The present study was designed to determine whether these criteria could be accurately applied to the resting 12 lead electrocardiogram on which the degree of pre-excitation was variable. The Rosenbaum criteria correctly identified a left sided accessory pathway in 26 of 34 patients and a right-sided accessory pathway in nine of 13 patients. The Gallagher and World Health Organisation criteria correctly identified the location in only 15 (32%) of the 47 patients. The resting vectorcardiogram was inaccurate for locating the accessory pathway.

Although published criteria are useful for identifying the site of the accessory pathway from an electrocardiogram obtained when rapid atrial pacing is being used to achieve maximal pre-excitation, they are not suitable for identifying the exact site of an accessory pathway from the resting 12 lead electrocardiogram.

The electrocardiogram from patients with the Wolff-Parkinson-White syndrome[1–3] classically demonstrates a short PR interval, a broad QRS complex, and typical slurring of the initial portion of the QRS complex, referred to as a delta wave.[4] The PR interval and the width of the QRS complex, or degree of pre-excitation, may vary[2 3] depending on the location of the accessory pathway; the intra-atrial, atrioventricular node, His-Purkinje, and accessory pathway conduction times; autonomic tone; and cardioactive medications.[2 3 5] These factors may result in a spectrum of findings, including no apparent pre-excitation, varying degrees of

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pre-excitation, or maximal pre-excitation, on the resting 12 lead electrocardiogram in patients with the Wolff-Parkinson-White syndrome.

Before electrophysiological testing, knowledge of the location of an accessory pathway is useful because it may be important initial evidence of multiple accessory pathways, especially in patients who have one pathway that conducts only in the anterograde direction and accounts for the delta wave and a second pathway that conducts only in the retrograde direction and participates in reentrant tachycardia (concealed accessory pathway).[6] Criteria for locating the accessory pathway from the 12 lead electrocardiogram have been published.[1-3] These criteria[2 3] were derived from electrocardiograms demonstrating maximal pre-excitation. This often requires rapid atrial pacing. The use of such criteria to determine accurately the location of the accessory pathway from the resting electrocardiogram has not previously been assessed and forms the basis for this study.

Patients and methods

PATIENTS

Between 1976 and 1985, 47 patients (32 male and 15 female) with the Wolff-Parkinson-White syndrome met the following criteria for entry into this study: (*a*) presence of a delta wave on the resting 12 lead electrocardiogram; (*b*) presence of a single anterograde conducting accessory pathway found at preoperative electrophysiological study and confirmed by epicardial mapping during operation; and (*c*) loss of pre-excitation after surgical division of the accessory pathway. The mean age of the patients was 28 years (range 7–65 years). Eight patients had associated cardiac disorders: dilated cardiomyopathy and left lateral accessory pathway in one, atrial septal defect and left paraseptal accessory pathway in one, and Ebstein's anomaly with a right-sided accessory pathway in six. Four patients had hypertension.

ELECTROCARDIOGRAM

The resting 12 lead electrocardiogram was recorded at 25 mm/s and a gain of 10 mm/mV. All patients were in sinus rhythm, and the mean heart rate was 71 beats/min (range 47–113 beats/min). If multiple electrocardiograms were obtained from a patient, the one demonstrating the most pre-excitation was chosen for analysis. All recordings were analysed by two of us. The delta wave polarity was recorded as being positive, negative, or isoelectrical during the first 40 ms of the beginning of the QRS complex (positive, most or all of the initial slurring with a positive deflection; negative, most or all of the initial slurring with a negative deflection; and isoelectrical, no slurring of the initial part of the QRS or an initial downward or upward deflection followed by a reversed deflection to the baseline during the first 40 ms of the QRS complex).

In 32 patients, three simultaneous channels of the electrocardiogram were recorded. These were grouped as follows: I, II, and III; aVR, aVL, and aVF; V1, V2, and V3; and V4, V5, and V6. In these patients the onset of the delta wave was determined as the time when the initial deflection was observed in one of the three simultaneously recorded leads. In the 15 remaining patients, the recordings were not simultaneous, and the delta wave was analysed independently in each lead.

VECTORCARDIOGRAM

The vectorcardiogram was obtained simultaneously with the 12 lead electrocardiogram in each patient. Computer analysis allowed for determination of the vector direction at 10, 20, 30, and 40 ms, with a mean vector at 30 ms (R30).

ELECTROPHYSIOLOGICAL EVALUATION AND EPICARDIAL MAPPING

Each patient had electrophysiological testing with methods that have previously been reported.[7 8] Left-sided accessory pathways were located by means of recordings of left atrial and left ventricular electrograms from an electrode catheter placed in the coronary sinus, and right-sided accessory pathways were located by a mapping electrode catheter during ventricular pacing and reciprocating tachycardia.[9] Epicardial mapping was performed at the time of operation[8-10] in all patients. The ventricular epicardial activation sequences were recorded dur-

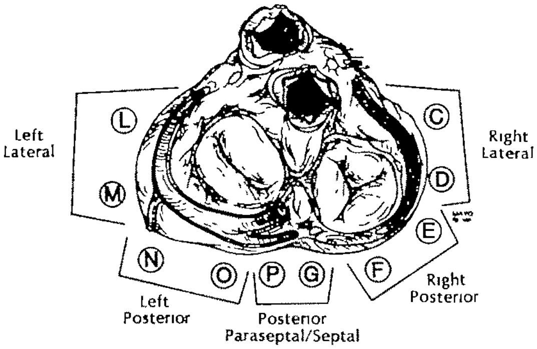


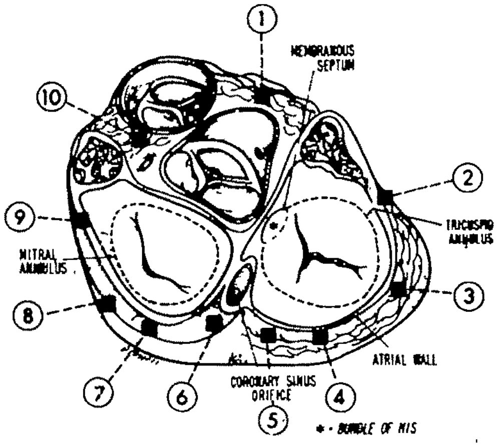
Fig 1 *Schematic drawing at the level of the mitral and tricuspid valves, demonstrating epicardial locations during intraoperative electrophysiological mapping (C–G, L–P) to locate accessory atrioventricular pathway. (By permission of the Mayo Foundation.)*

Table 1 *World Health Organisation task force criteria for locating the accessory atrioventricular pathway by the resting 12 lead electrocardiogram*

Condition statements	
(S1)	Delta wave (initial QRS) positive in I
(S2)	Delta wave positive in V1
(S3)	Delta wave negative in V1
(S4)	Delta wave isoelectrical in V1
(S5)	Q or QS waves in I and V6
(S6)	Q or QS waves in III and aVF
(S7)	Main QRS positive in III
(S8)	Main QRS negative in III
(S9)	Main QRS positive in V1
(S10)	Main QRS negative in V1
(S11)	Delta wave positive in II and aVF and positive or isoelectrical in III
(S12)	Delta wave negative in II, III, aVF
(S13)	Delta wave positive from V2 until V6
(S14)	Delta wave negative or isoelectrical in V6
(S15)	QRS configuration rS in V1 and Rs in V2

Criterion for anterior right ventricular pre-excitation:
S1 and S4 and S8 and S10
Criterion for posterior right ventricular pre-excitation.
S3 and S6 and S8 and S10
Criterion for posterior left ventricular pre-excitation:
S1 and S2 and S6 and S8 and S9 and S14
Criterion for lateral left ventricular pre-excitation:
S2 and S5 and S7 and S14
Criterion for anterior paraseptal pre-excitation:
S1 and S4 and S11
Criterion for posterior paraseptal pre-excitation:
S1 and S12 and S13 and S15

From Willems *et al*[3] by permission of the American College of Cardiology.



1 RIGHT ANTERIOR PARASEPTAL
2 RIGHT ANTERIOR
3 RIGHT LATERAL
4 RIGHT POSTERIOR
5 RIGHT PARASEPTAL
6 LEFT POSTERIOR PARASEPTAL
7 LEFT POSTERIOR
8 LEFT LATERAL
9 LEFT ANTERIOR
10 LEFT ANTERIOR PARASEPTAL

DELTA WAVE POLARITY

	I	II	III	AVR	AVL	AVF	V1	V2	V3	V4	V5	V6
①	+	+	+(±)	-	±(+)	+	±	±	+(±)	+	+	+
②	+	+	-(±)	-	+(±)	±(-)	±	+(±)	+(±)	+	+	+
③	+	±(-)	-	-	+	-(±)	±	±	±	+	+	+
④	+	-	-	-	+	-	±(+)	±	+	+	+	+
⑤	+	-	-	-(+)	+	-	±	+	+	+	+	+
⑥	+	-	-	-	+	-	+	+	+	+	+	+
⑦	+	-	-	±(+)	+	-	+	+	+	+	+	-(±)
⑧	-(±)	±	±	±(+)	-(±)	±	+	+	+	+	-(±)	-(±)
⑨	-(±)	+	+	-	-(±)	+	+	+	+	+	+	+
⑩	+	+	+(±)	-	±	+	±(+)	+	+	+	+	+

± = Initial 40 ms delta wave isoelectric
+ = Initial 40 ms delta wave positive
- = Initial 40 ms delta wave negative

Fig 2 *Electrocardiographic classification of Wolff-Parkinson-White syndrome as defined by Gallagher et al.*[2] *Ten representative sites are depicted on a cross section of ventricles at level of atrioventricular rings. Expected polarity of delta waves resulting from pre-excitation at these sites is indicated for each of the 12 standard leads, based on analysis of mean initial forces (40 ms) of ventricular depolarisation. (From Gallagher et al.*[2] *By permission of Grune and Stratton.)*

ing sinus rhythm and atrial pacing from a site close to the accessory pathway. Atrial activation was determined during ventricular pacing and reciprocating tachycardia in all patients. The site of the accessory pathway was classified as: left lateral, left posterior, posterior paraseptal/septal, right posterior, and right lateral (fig 1).

The surgical approach to division of the accessory pathway has been described elsewhere.[8 10] In all patients division of the accessory pathway at the site corresponding to the earliest epicardial activation resulted in disappearance of pre-excitation. This was demonstrated by the surface electrocardiogram, the absence of pre-excitation during incremental atrial pacing, and the presence of type 1 second degree atrioventricular block during atrial pacing.

PUBLISHED CRITERIA FOR LOCATING THE ACCESSORY PATHWAY

In all patients the preoperative resting electrocardiogram was compared with the following criteria: (*a*) Rosenbaum criteria[1] (Wolff-Parkinson-White type A, in which there is a predominantly positive QRS complex in V1 and V2, and Wolff-Parkinson-White type B, in which there is a predominantly negative QRS complex in V1 and V2; (*b*) Gallagher criteria[2] (delta wave polarity, as recorded during rapid atrial pacing resulting in maximal pre-excitation during the electrophysiological study (fig 2)); and (*c*) World Health Organisation criteria,[3] which are a composite of previous criteria (table 1). We did not require complete concordance between all of the criteria for identification of the site of a pathway: with the Gal-

Table 2 *Delta wave polarity on the resting 12 lead electrocardiogram in patients with left lateral or left posterior accessory pathways*

		*Lead**													*Concordance of criteria‡*	
Accessory pathway location	*Patient*	*I*	*II*	*III*	*R*	*L*	*F*	*V1*	*V2*	*V3*	*V4*	*V5*	*V6*	*Type of WPW†*[1]	*Gallagher*[2]	*WHO*[3]
Left lateral, QRS > 120 ms	1	+	±	±	±	±	±	+	+	+	+	+	±	A	Y	N
	2	±	+	+	±	±	+	+	+	+	+	+	±	A	N	Y
	3	+	−	−	−	+	−	+	+	+	+	+	±	A	N	N
	4	±	+	+	−	−	+	+	+	+	+	+	+	B	N	N
	5	±	+	+	−	±	+	+	+	+	+	+	+	A	N	N
	6	+	+	+	−	±	+	+	+	+	+	+	+	B	N	N
	7	+	±	±	−	±	±	+	+	+	+	±	±	A	Y	N
	8	−	+	+	±	−	+	+	+	+	+	+	±	A	N	Y
Left lateral, QRS < 120 ms	1	±	±	±	±	±	±	+	+	+	+	±	±	B	Y	N
	2	−	+	+	−	−	+	+	+	+	+	+	±	A	N	Y
	3	±	+	+	±	−	+	±	±	±	+	+	±	B	N	N
	4	±	+	+	±	−	+	+	+	+	+	+	±	A	N	Y
	5	±	+	+	±	−	+	+	+	±	+	+	+	B	N	N
	6	±	+	+	−	−	+	+	+	+	+	+	+	A	N	N
	7	−	±	±	±	±	±	+	+	+	+	±	−	A	Y	Y
	8	±	+	+	±	±	+	±	+	±	+	±	±	A	N	N
	9	+	+	+	−	±	+	+	+	+	+	+	+	A	N	N
	10	+	+	−	−	+	±	±	±	+	+	+	±	A	N	N
Left posterior, QRS > 120 ms	1	±	±	±	±	+	±	+	+	+	+	±	±	A	N	N
	2	±	+	+	−	±	+	+	+	+	+	+	+	A	N	N
	3	±	±	±	±	±	±	+	+	+	+	±	−	A	N	Y
	4	+	±	±	−	±	±	+	+	+	+	+	+	A	N	N
	5	+	±	−	−	+	±	+	+	+	+	+	+	A	N	Y
	6	+	+	−	−	+	±	±	+	+	+	+	+	A	N	N
	7	+	+	+	−	+	+	+	+	+	+	+	+	A	N	N
Left posterior, QRS < 120 ms	1	−	+	+	±	−	+	+	+	+	+	±	±	B	N	N
	2	±	+	+	−	±	+	+	+	+	+	+	+	A	N	N
	3	±	±	±	±	±	±	±	±	+	+	+	±	A	N	N
	4	−	+	+	±	−	+	+	+	+	+	+	±	A	N	N
	5	+	−	−	−	+	−	±	+	+	+	+	±	A	Y	N
	6	±	±	±	±	±	±	±	±	+	+	+	±	B	N	N

*+, positive delta wave; −, negative delta wave, ±, isoelectric delta wave
†WPW, Wolff-Parkinson-White syndrome.
‡N, no (criteria did not identify location of pathway); Y, yes (criteria did identify location of pathway).

Table 3 *Usefulness of established criteria to locate the accessory pathway by the resting 12 lead electrocardiogram in patients with the Wolff-Parkinson-White syndrome*

			Gallagher criteria[2]			*World Health Organisation criteria*[3]		
Accessory pathway location	*No of patients*	*Rosenbaum criteria*[1] *(type of WPW* and No of patients)*	*Location correctly identified (No of patients)*	*Best correlations†*	*Worst correlations‡*	*Location correctly identified (No of patients)*	*Best correlations†*	*Worst correlations‡*
Left lateral	18	A, 13 B, 5	4	+V1 to V4 ±V6	±II, III, F −V6, ± −V5	5	+V1, ±V6 +QRS$_{III}$	Q–QS$_{I, V6}$ −V6
Left posterior	13	A, 11 B, 2	1	+V1 to V5	−II, III, F, +I, L −V6	2	+V1 +QRS$_{V1}$	−V6, +I −QRS$_{III}$
Posterior paraseptal/septal	9	*Left* A, 2 B, 1 *Right* A, 3 B, 3	2 3	*Left* +I, L, V1 to V5 −II, III, F *Right* +I, L, V2 to V5 −II, III, F	+V6, −R ±V1	2	−II, III, F +I	+V2 to V6 rS$_{V1}$, RS$_{V2}$
Right posterior	3	A, 1 B, 2	3	+I, L, V3 to V6 ±V1 −II, III, F, R	±V2	3	Q–QS$_{III, F}$ −QRS$_{III, V1}$	−V1
ight lateral	4	B, 4	2	+I, L, V4 to V6 −III, F, R	±(−) II ±V1 to V2	3	−QRS$_{III, V1}$ +I	±V1

+, positive delta wave;
−, negative delta wave;
±, isoelectric delta wave;
*WPW, Wolff-Parkinson-White syndrome.
≥60% of electrocardiograms had these findings.
≤40% of electrocardiograms had these findings.

Table 4 *Vector direction at 10, 20, 30, and 40 ms on the resting vectorcardiogram in patients with left lateral or left posterior accessory pathways*

		*Frontal**					*Sagittal†*					*Horizontal‡*				
Accessory pathway location	*Patient*	*10*	*20*	*30*	*R30§*	*40*	*10*	*20*	*30*	*R30§*	*40*	*10*	*20*	*30*	*R30§*	*40*
Left lateral, QRS > 120 ms	1	L	R	R	R	L	S	I	I	I	I	A	A	A	A	A
	2	N	R	L	L	L	I	I	I	I	I	A	A	A	A	A
	3	L	L	L	L	L	I	S	S	S	S	A	A	A	A	A
	4	R	L	L	L	L	I	I	I	I	I	A	A	A	A	A
	5	L	L	R	L	R	NA	NA	NA	NA	NA	A	A	A	A	A
	6	L	L	L	L	L	NA	NA	NA	NA	NA	A	A	A	A	A
	7	L	L	L	L	L	I	I	I	I	I	A	A	A	A	A
	8	R	R	R	R	R	I	I	I	I	I	A	A	A	A	A
Left lateral, QRS < 120 ms	1	R	R	R	R	R	I	N	I	I	S	A	A	A	A	A
	2	R	L	L	L	L	I	S	S	S	I	A	A	A	A	A
	3	R	R	R	R	L	I	I	I	I	I	A	A	A	A	A
	4	L	L	L	L	R	I	I	I	I	I	A	A	A	A	A
	5	L	L	L	L	L	NA	NA	NA	NA	NA	A	A	A	A	A
	6	L	L	L	L	L	I	I	I	I	I	A	A	A	A	A
	7	L	R	R	R	R	NA	NA	NA	NA	NA	A	A	A	A	A
	8	L	L	L	L	R	NA	NA	NA	NA	NA	A	A	A	A	A
	9	L	L	L	L	L	I	I	I	I	I	A	A	A	A	A
	10	L	L	L	L	L	NA	NA	NA	NA	NA	A	A	A	A	A
Left posterior, QRS > 120 ms	1	N	L	L	L	L	I	I	N	I	S	A	A	A	A	A
	2	L	L	L	L	L	I	I	I	I	I	A	A	A	A	A
	3	R	R	R	R	R	I	I	S	N	S	A	A	A	A	A
	4	R	R	N	R	L	NA	NA	NA	NA	NA	A	A	A	A	A
	5	L	L	L	L	L	S	S	S	S	S	A	A	A	A	A
	6	L	L	L	L	L	I	I	I	I	I	A	A	A	A	A
	7	L	L	L	L	L	I	I	I	I	I	A	A	A	A	A
Left posterior, QRS < 120 ms	1	R	R	L	R	L	I	I	I	I	I	A	A	A	A	A
	2	L	L	L	L	L	I	I	I	I	I	A	A	A	A	A
	3	L	L	L	L	R	I	I	I	I	S	A	A	A	A	A
	4	L	L	R	R	L	NA	NA	NA	NA	NA	A	A	A	A	A
	5	L	L	L	L	L	NA	NA	NA	NA	NA	A	A	A	A	A
	6	L	L	L	L	L	NA	NA	NA	NA	NA	A	A	A	A	A

*L, left; R, right, N, neutral. †I, inferior; S, superior; NA, not available ‡A, anterior. §R30, mean vector of first 30 ms.

Table 5 *Delta wave polarity on the resting 12 lead electrocardiogram in patients with posterior paraseptal, right posterior, or right lateral accessory pathways*

		*Lead**													*Concordance of criteria‡*	
Accessory pathway location	*Patient*	*I*	*II*	*III*	*R*	*L*	*F*	*V1*	*V2*	*V3*	*V4*	*V5*	*V6*	*Type of WPW†*^{1}	*Gallagher*^{2}	*WHO*^{3}
Left posterior paraseptal, QRS > 120 ms	1	+	−	−	±	+	−	+	+	+	+	±	±	A	Y	N
	2	+	−	−	+	±	−	−	−	−	+	+	+	B	N	N
	3	+	−	−	±	+	−	+	+	+	+	+	±	A	Y	N
Right posterior paraseptal, QRS > 120 ms	1	+	−	−	−	+	−	±	+	+	+	+	+	B	Y	Y
	2	+	±	±	−	+	±	+	+	+	+	+	+	A	N	N
	3	+	−	−	±	+	−	+	+	+	±	±	±	B	N	N
	4	+	−	−	±	+	−	+	+	+	+	+	+	A	Y	Y
	5	+	±	−	−	+	±	−	+	+	+	+	±	A	N	N
	6	+	−	−	−	+	−	±	+	+	+	+	±	B	Y	N
Right posterior, QRS > 120 ms	1	+	−	−	−	+	−	±	+	+	+	+	+	B	Y	Y
	2	+	±	−	−	+	−	±	+	+	+	+	+	A	Y	Y
Right posterior, QRS < 120 ms	1	+	−	−	−	+	−	+	+	+	+	+	+	B	Y	Y
Right lateral, QRS > 120 ms	1	+	+	−	−	+	−	+	+	+	+	+	+	B	N	Y
	2	+	+	+	−	±	+	−	±	±	+	+	+	B	N	N
	3	+	−	−	±	+	−	±	+	+	+	+	+	B	Y	Y
Right lateral, QRS < 120 ms	1	+	+	−	−	+	−	+	+	±	+	+	+	B	Y	Y

*+, positive delta wave; −, negative delta wave; ±, isoelectric delta wave.
†WPW, Wolff-Parkinson-White syndrome
‡N, no (criteria did not identify location of pathway); Y, yes (criteria did identify location of pathway).

Table 6 *Vector direction at 10, 20, 30, and 40 ms on the resting vectorcardiogram in patients with posterior paraseptal, right posterior, or right lateral accessory pathways*

		Frontal					*Sagittal*					*Horizontal*				
Accessory pathway location	*Patient*	*10*	*20*	*30*	*R30*	*40*	*10*	*20*	*30*	*R30*	*40*	*10*	*20*	*30*	*R30*	*40*
Left posterior paraseptal, QRS > 120 ms	1	L	L	L	L	L	S	S	S	S	S	A	A	A	A	A
	2	R	L	L	L	L	I	I	I	I	S	P	P	P	P	P
	3	L	L	L	L	L	NA	NA	NA	NA	NA	A	A	A	A	A
Right posterior paraseptal, QRS > 120 ms	1	L	L	L	L	L	I	I	S	S	S	A	A	A	A	A
	2	L	L	L	L	L	N	N	S	S	S	A	A	A	A	A
	3	R	L	L	L	L	S	S	S	S	S	A	A	P	A	P
	4	L	L	L	L	L	NA	NA	NA	NA	NA	A	A	P	A	A
	5	L	L	L	L	L	NA	NA	NA	NA	NA	P	P	P	P	P
	6	L	L	L	L	L	I	S	S	S	S	A	A	P	P	P
Right posterior, QRS > 120 ms	1	L	L	L	L	L	—	—	S	S	S	A	A	A	A	P
	2	L	L	L	L	L	NA	NA	NA	NA	NA	P	N	A	A	A
Right posterior, QRS < 120 ms	1	R	L	L	L	L	NA	NA	NA	NA	NA	A	A	A	A	A
Right lateral, QRS > 120 ms	1	R	R	L	R	L	N	S	S	S	S	A	A	A	A	A
	2	L	L	L	L	L	I	I	I	I	I	A	P	P	P	P
	3*															
Right lateral, QRS < 120 ms	1	L	L	L	L	L	S	S	S	S	S	A	P	A	A	A

*The vector was not obtained for this patient.
L, left; R, right, I, inferior; S, superior, NA, not available, N, neutral; A, anterior, P, posterior; R30, mean vector of first 30 ms.

lagher criteria an accessory pathway location was correctly identified by the 12 lead electrocardiogram if the polarity of the delta wave in at least nine of the 12 leads conformed with the published criteria (fig 2); and for the World Health Organisation criteria[3] an accessory pathway location was correctly identified by the 12 lead electrocardiogram if all of the criteria (table 1) except one were correct.

Results

LEFT LATERAL ACCESSORY PATHWAY

Type A Wolff-Parkinson-White syndrome was present in 13 of the 18 patients (table 2). The pathway location was correctly identified by the Gallagher criteria[2] in four of the patients and by the World Health Organisation criteria[3] in five (table 3).

The vector for R30 (table 4) was anterior in all 18 patients, oriented to the left in 13 of the patients, and inferior in 10 of the 12 patients for whom such information was available.

LEFT POSTERIOR ACCESSORY PATHWAY

Type A Wolff-Parkinson-White syndrome was present in 11 of the 13 patients (table 2). The pathway location was correctly identified by the Gallagher criteria[2] in one patient and by the World Health Organisation criteria[3] in two (table 3).

The vector for R30 (table 4) was anterior in all patients, oriented to the left in nine of the 13 patients, and inferior in seven of the nine patients for whom such information was available.

POSTERIOR PARASEPTAL ACCESSORY PATHWAY (TABLE 5)

Type A Wolff-Parkinson-White syndrome was present in two of the three patients with a left posterior paraseptal accessory pathway and three of the six with a right posterior paraseptal accessory pathway. The pathway location was correctly identified by the Gallagher criteria[2] in five of the nine patients and by the World Health Organisation criteria[3] in two (table 3).

The vector for R30 (table 6) was anterior in six of the nine patients, oriented to the left in all nine patients, and superior in five of the six patients for whom such information was available.

RIGHT POSTERIOR ACCESSORY PATHWAY (TABLE 5)

Type B Wolff-Parkinson-White syndrome was present in two of the three patients. All three patients had the pathway location correctly identified by the Gallagher criteria[2] and the World Health Organisation criteria[3] (table 3).

The vector for R30 (table 6) was anterior in all three patients, oriented to the left in all three patients, and superior in the one patient for whom such information was available.

RIGHT LATERAL ACCESSORY PATHWAY (TABLE 5)

Type B Wolff-Parkinson-White syndrome was present in all four patients. The pathway location was correctly identified by the Gallagher criteria[2] in two of the four patients and by the World Health Organisation criteria[3] in three (table 3).

The vector for R30 (table 6) was anterior in two of the patients, oriented to the left in two of the patients, and superior in two of the patients. A vector was not obtained in the fourth patient.

Discussion

The concept that pre-excitation in Wolff-Parkinson-White syndrome was the result of conduction over an accessory atrioventricular pathway remained speculative until 1967 when Durrer and Roos provided evidence for atrioventricular conduction over an accessory pathway by epicardial mapping of the heart.[11] Work by Burchell *et al*[12] and Boineau and Moore[13] further substantiated this belief, and in 1968, Cobb *et al*[14] and Sealy *et al*[15] were the first to divide an accessory pathway successfully. Because the Wolff-Parkinson-White syndrome can be cured by surgical ablation the ability to locate the site of pre-excitation has become of great importance.

Electrocardiography and vectorcardiography[16-18] have remained the two most widely used methods to predict the location of the accessory pathway. Recently, echocardiography,[19] body surface mapping,[20 21] phase imaging,[22] and the moving dipole[23] have also been used in an attempt to locate the site of an accessory pathway.

TYPE A AND TYPE B WOLFF-PARKINSON-WHITE SYNDROME

The classification by Rosenbaum *et al*[1] of Wolff-Parkinson-White syndrome into type A or type B has stood the test of time because of its simplicity. Type A was believed to be due to left posterobasal pre-excitation, and type B to right lateral pre-excitation.[24] The Rosenbaum criteria correctly identified a left-sided accessory pathway in 76% of our patients and a right-sided accessory pathway in 69% of our patients. This classification, however, does not help to separate free wall and paraseptal/septal locations.

VECTORCARDIOGRAPHY IN WOLFF-PARKINSON-WHITE SYNDROME

Vectorcardiography has also been used to locate the accessory pathway. In this study it did not accurately identify the location of the accessory pathway because (*a*) the vector was anterior in most (89%) of the patients; (*b*) the vector was to the left in 71% of the patients with a left free wall accessory pathway, in all patients with a posterior paraseptal accessory pathway, and in 83% of the patients with a right posterior or right lateral accessory pathway; and (*c*) the vector was inferior in 81% of the patients with a left free wall accessory pathway, superior in 83% of the patients with a posterior paraseptal accessory pathway, and superior in 75% of the patients with a right free wall accessory pathway.

These findings do not support a previous study that suggested a vector directed anteriorly and to the right indicated a left lateral accessory pathway and a vector directed to the left and anteriorly indicated a paraseptal accessory pathway.[25] The suggestion in another study that a left lateral accessory pathway had a 10 ms vector directed inferiorly and a 20 ms vector directed to the right[26] was not confirmed by our study.

ELECTROCARDIOGRAPHY AND EPICARDIAL MAPPING CORRELATIONS

Epicardial mapping during operation provides an opportunity for a comparison with the results of the non-invasive determination of accessory pathway location. Boineau *et al*, Frank, and Gallagher *et al*, using 12 lead electrocardiography,[5 27 28] and Tonkin *et al*, using vectorcardiography,[26] provided the first correlations. However, criteria for locating the accessory pathway from the 12 lead electrocardiogram based on the delta wave polarity were not adopted until the important article by Gallagher *et al*.[2] Their review provided information relating the delta wave polarity in the 12 standard leads obtained during rapid atrial pacing (resulting in maximal pre-excitation) to the accessory pathway location determined by epicardial mapping during operation for 10 different accessory pathway locations. They suggested that their results should be applied to patients in whom the QRS complexes were more than 140 ms.

Recently, the World Health Organisation[3] developed a classification of accessory pathway location according to the 12 lead electrocardiogram from a composite of previous studies[1 2 5 29] and suggested six sets of criteria for accessory pathway location. Because of fusion caused by conduction over the atrioventricular node and the accessory pathway, they found that pre-excitation and the width of the QRS complex may vary but they did not strictly limit the classification to a certain QRS width. From a practical standpoint, patients with the Wolff-Parkinson-White syndrome who clearly have pre-excitation on the resting 12 lead electrocardiogram often have a QRS width of less than 120 ms. In our series, 18 of the 47 patients had a QRS width of less than 120 ms and only 10 had a QRS of 140 ms or more.

The previously reported criteria[2 3] were developed and are useful for identifying the accessory pathway location from an electrocardiogram obtained during maximal pre-excitation, which often requires atrial pacing. Our study shows that the previously reported criteria for accessory pathway location cannot be applied accurately to the resting 12 lead electrocardiogram. Only 32% of the patients in our series showed concordance with the Gallagher and World Health Organisation criteria. Both sets of criteria were inaccurate for left free wall and posterior paraseptal pathway locations. The results obtained in patients with a QRS width of more than 120 ms were not different from those in patients with a width of less than 120 ms.

The results in our study differ from previous criteria[2,3] as follows: (*a*) a negative delta wave or a Q wave in V6 rarely occurs and should not be considered necessary for locating a left lateral or left posterior accessory pathway[2,3,27,28]; (*b*) inferior leads II, III, and aVF often have a positive delta wave in the left lateral and left posterior accessory pathway[27,28]; (*c*) a negative QRS complex in leads V1 and III does not permit right lateral and right posterior accessory pathways to be discriminated; and (*c*) the combination of a positive QRS complex in lead V1 and a negative QRS complex in lead III rarely occurs with a left posterior accessory pathway.

The limitations of our study are as follows: (*a*) in 15 of the 47 patients the delta wave was not analysed simultaneously in any lead, but great care was taken to analyse the first 40 ms of ventricular activation in each lead; and (*b*) the number of right-sided accessory pathways was small and no patients with anterior septal pathways were evaluated.

Clinical implications

The resting 12 lead electrocardiogram is not helpful for identifying the precise location of an accessory pathway by published criteria. If such information is required, detailed electrophysiological testing should be performed.

References

1 Rosenbaum FF, Hecht HH, Wilson FN, Johnston FD. The potential variations of the thorax and the esophagus in anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome). *Am Heart J* 1945;**29**:281–326.

2 Gallagher JJ, Pritchett ELC, Sealy WC, Kasell J, Wallace AG. The preexcitation syndromes. *Prog Cardiovasc Dis* 1978;**20**:285–327.

3 Willems JL, Robles de Medina EO, Bernard R, *et al.* Criteria for intraventricular conduction disturbances and pre-excitation. *J Am Coll Cardiol* 1985;**5**: 1261–75.

4 Wolff L, Parkinson J, White PD. Bundle-branch block with short P–R interval in healthy young people prone to paroxysmal tachycardia. *Am Heart J* 1930;**5**:685–704.

5 Boineau JP, Moore EN, Spear JF, Sealy WC. Basis of static and dynamic electrocardiographic variations in Wolff-Parkinson-White syndrome: anatomic and electrophysiologic observations in right and left ventricular preexcitation. *Am J Cardiol* 1973;**32**:32–45.

6 Hammill SC, Pritchett ELC, Klein GJ, Smith WM, Gallagher JJ. Accessory atrioventricular pathways that conduct only in the antegrade direction. *Circulation* 1980;**62**:1335–40.

7 Hammill SC, Holmes DR Jr, Wood DL, *et al.* Electrophysiologic testing in the upright position: improved evaluation of patients with rhythm disturbances using a tilt table. *J Am Coll Cardiol* 1984;**4**:65–71.

8 Holmes DR Jr, Danielson GK, Gersh BJ, *et al.* Surgical treatment of accessory atrioventricular pathways and symptomatic tachycardia in children and young adults. *Am J Cardiol* 1985;**55**:1509–12.

9 Gallagher JJ, Pritchett ELC, Benditt DG, *et al.* New catheter techniques for analysis of the sequence of retrograde atrial activation in man. *Eur J Cardiol* 1977;**6**:1–14.

10 Holmes DR Jr, Osborn MJ, Gersh B, Maloney JD, Danielson GK. The Wolff-Parkinson-White syndrome: a surgical approach. *Mayo Clin Proc* 1982;**57**:345–50.

11 Durrer D, Roos JP. Epicardial excitation of the ventricles in a patient with Wolff-Parkinson-White syndrome (type B). *Circulation* 1967;**35**:15–21.

12 Burchell HB, Frye RL, Anderson MW, McGoon DC Atrioventricular and ventriculoatrial excitation in Wolff-Parkinson-White syndrome (type B): temporary ablation at surgery. *Circulation* 1967;**36**.663–72

13 Boineau JP, Moore EN. Evidence for propagation of activation across an accessory atrioventricular connection in types A and B pre-excitation. *Circulation* 1970;**41**:375–97.

14 Cobb FR, Blumenschein SD, Sealy WC, Boineau JP, Wagner GS, Wallace AG. Successful surgical interruption of the bundle of Kent in a patient with Wolff-Parkinson-White syndrome. *Circulation* 1968;**38**:1018–29.

15 Sealy WC, Hattler BG Jr, Blumenschein SD, Cobb FR. Surgical treatment of Wolff-Parkinson-White syndrome. *Ann Thorac Surg* 1969;**8**:1–10.

16 Bleifer S, Kahn M, Grishman A, Donoso E. Wolff-Parkinson-White syndrome: a vector cardiographic, electrocardiographic and clinical study *Am J Cardiol* 1959;**4**:321–33.

17 Tranchesi J, Guimarães AC, Teixeira V, Pileggi F. Vectorial interpretation of the ventricular complex in Wolff-Parkinson-White syndrome. *Am J Cardiol* 1959;**4**:334–40.

18 Lowe KG, Emslie-Smith D, Ward C, Watson H. Classification of ventricular pre-excitation: vectorcardiographic study. *Br Heart J* 1975;**37**:9–19.

19 Windle JR, Armstrong WF, Feigenbaum H, Miles WM, Prystowsky EN. Determination of the earliest site of ventricular activation in Wolff-Parkinson-White syndrome: application of digital continuous loop two-dimensional echocardiography. *J Am Coll*

Cardiol 1986;7:1286–94.

20 Benson DW Jr, Sterba R, Gallagher JJ, Walston A II, Spach MS. Localization of the site of ventricular preexcitation with body surface maps in patients with Wolff-Parkinson-White syndrome. *Circulation* 1982; 65:1259–68.

21 Groenewegen AS, Spekhorst HHM, Reek EJ. A quantitative method for the localization of the ventricular pre-excitation area in the Wolff-Parkinson-White syndrome using singular value decomposition of body surface potentials. *J Electrocardiol* 1985; 18:157–67.

22 Rakovec P, Kranjec I, Fettich J, *et al*. Localization of accessory pathways in Wolff-Parkinson-White syndrome by phase imaging. *Cardiology* 1983;70: 138–44.

23 Gulrajani RM, Pham-Huy H, Nadeau RA, *et al*. Application of the single moving dipole inverse solution to the study of the Wolff-Parkinson-White syndrome in man. *J Electrocardiol* 1984;17:271–87.

24 Giraud G, Latour H, Puech P, Roujon J. Les troubles de rythme du syndrome de Wolff-Parkinson-White. Analyse électrocardiographique endocavitaire. *Arch Mal Coeur* 1956;49:101–33.

25 Talwar KK, Blomstrom P, Edvardsson N, William-Olsson G, Olsson SB. Spatial vectorcardiography in the Wolff-Parkinson-White syndrome: correlation with epicardial mapping findings. *PACE* 1984; 7:979–84.

26 Tonkin AM, Wagner GS, Gallagher JJ, Cope GD, Kasell J, Wallace AG. Initial forces of ventricular depolarization in the Wolff-Parkinson-White syndrome: analysis based upon localization of the accessory pathway by epicardial mapping. *Circulation* 1975;52:1030–6.

27 Frank R. Apport des investigations endocavitaires et de cartographies epicardiques dans l'étude des syndromes de pré-excitation ventriculaire. Thése pour le Doctorat de Medicine: Paris, Editions Medicals et Universitaires, 1974.

28 Gallagher JJ, Svenson RH, Sealy WC, Wallace AG. The Wolff-Parkinson-White syndrome and the preexcitation dysrhythmias: medical and surgical management. *Med Clin North Am* 1976; 60:101–23.

29 Wellens HJJ, Durrer D. The role of an accessory atrioventricular pathway in reciprocal tachycardia: observations in patients with and without the Wolff-Parkinson-White syndrome. *Circulation* 1975;52:58–72.

Br Heart J 1987;58:333–8

Electrophysiological action of bepridil on atrioventricular accessory pathways

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SUMMARY The electrophysiologic properties of bepridil, a calcium channel blocker with additional effects on fast response tissues, were investigated in 10 patients with atrioventricular accessory pathways. Seven patients had Wolff-Parkinson-White syndrome, and three had concealed atrioventricular pre-excitation. A dose of 4 mg/kg was administered intravenously over five minutes. Bepridil increased the AH interval and the functional refractory period of the atrioventricular node. The effective refractory periods of the right atrium and right ventricle were also increased. Bepridil prolonged refractoriness in the accessory pathway both in the anterograde and retrograde direction. After bepridil administration it was impossible to induce reciprocating tachycardia electrically in two patients because of conduction block in the normal pathway. On the other hand, the zone of tachycardia was often increased after bepridil. Nevertheless, the heart rate during tachycardia was slowed by depression of conduction in both the normal and accessory pathways.

The findings of this study provide a basis for the antiarrhythmic action of bepridil in patients with atrioventricular accessory pathways.

Bepridil, which was initially developed as an antianginal drug,[1-3] has been shown to have electrophysiological effects on the heart. As a calcium antagonist the compound depresses slow responses in the sinus node and the atrioventricular node.[4] In vitro studies, however, have also shown that bepridil has class I antiarrhythmic activity and reduces the maximum rate of depolarisation in fast response tissues (myocardium, Purkinje fibres).[5] These findings are consistent with the widespread electrophysiological changes induced in the human heart by bepridil.[6-10] Preliminary reports have underlined the value of bepridil in the treatment of cardiac arrhythmias.[11-16] The present study was performed to evaluate the effects of bepridil on the Wolff-Parkinson-White syndrome and the associated reentry tachycardias.

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Patients and methods

We studied 10 patients (six men and four women) aged 14 to 55 years (mean 33). Seven had Wolff-Parkinson-White syndrome (type A in four and type B in three) and three had concealed pre-excitation with accessory pathways conducting only in the retrograde direction. Spontaneous episodes of tachycardia were found in nine patients (paroxysmal supraventricular tachycardia in seven and atrial fibrillation in two). There was no evidence of other heart disease in any of these patients. After informed consent, electrophysiological studies were performed on patients in the post-absorptive, non-sedated state. Cardioactive drugs were discontinued at least seven days before the study. None of the patients was receiving amiodarone.

We used the Seldinger technique to introduce four electrode catheters via the right and left femoral veins. Two were positioned in the right atrium, one to pace the upper septal region and the other to record a bipolar electrogram from the external wall. His bundle potential was measured with a tripolar

Table 1 *Effect of bepridil on normal conduction pathways and myocardial tissue (all values are ms)*

				AV node-His pathway							
				AH		*HV*		*AVN ERP*		*AVN FRP*	
Case No	*Age (yr) and sex*	*Type WPW*	*PCL*	*C*	*B*	*C*	*B*	*C*	*B*	*C*	*B*
1	55 F	A	500	110	120						
2	14 M	Concealed	500	45	50	45	50	<230	<230	310	370
3	41 F	B	500	100	100						
4	24 M	B	500	70	100						
5	19 F	A	600	110	120						
6	60 M	Concealed	400	90	105	85	85	<220	<240	340	370
7	32 F	B	500	110	120						
8	23 M	A	400								
9	50 M	Concealed	600	80	60	40	50	280	<250	360	360
10	21 M	A	500	70	80			<210	<280	280	330
Mean (1SD)				87 (23)	95 (26)	57 (25)	62 (20)			322 (35)	357 (19)
p value				>0·10						>0·05	

AVN, atrioventricular node; RA, right atrium; RV, right ventricle; ERP, effective refractory period; FRP, functional refractory period; C, control; B, bepridil, PCL, pacing cycle length.

catheter electrode.[17] The fourth catheter electrode was used to pace the right ventricular apex. In addition, a quadripolar catheter electrode was inserted via the left basilar vein and positioned in the coronary sinus to record left atrial activity. The proximal terminals of the His bundle catheter were connected to an electrocardiogram amplifier. Intracardiac electrograms were filtered between 50 and 700 Hz. We used an eight channel direct ink-jet recorder (Elema, Sweden) with paper speeds of 100 or 200 mm/s. Five external leads (I, II, III, V1, V6) were recorded simultaneously. Cardiac pacing was done by means of a programmable modular stimulator (Janssen, Belgium). Electrical impulses (1·5 ms) were delivered at twice diastolic threshold intensity. All data recorded throughout the study were stored on magnetic tape (Hewlett-Packard).

Electrical stimulation was applied successively to the atria and ventricles. Pacing at increasing rates was used to assess the functional properties of the conduction pathways.[18] Cardiac refractory periods were determined by the extrastimulus method.[19] During regular pacing of the heart, increasingly premature depolarisations were elicited every eighth complex (the coupling interval was reduced by 10 ms steps) until any response disappeared.

Electrically induced reciprocating tachycardias were analysed. The mode of onset and termination, cycle length, and conduction data were taken into account. Repeat studies were performed 10 minutes after intravenous administration of bepridil (4 mg/kg over five minutes). Blood samples were collected 10, 20, and 30 minutes after injection to measure plasma concentrations of bepridil. The results were analysed statistically by the Student *t* test for paired data.

Results

Table 1 shows the effects of bepridil on atrioventricular node-His conduction. The AH interval was determined before and after bepridil administration in nine patients. After bepridil the atrioventricular nodal conduction time was increased in seven patients, reduced in one patient, and unaltered in another. There was an insignificant mean increase of 8 ms in the AH interval. The effect on the HV interval was assessed in the three patients with concealed pre-excitation. The HV interval was increased in two patients by five and 10 ms respectively and unchanged in the third patient.

The effective refractory period of the atrioventricular node could not be measured accurately both before and after the drug in any of the patients. In four patients bepridil had measurable effects on the functional refractory period of the atrioventricular node. The refractoriness of the atrioventricular node was lengthened in three patients and unchanged in the fourth. The mean increase of 55 ms was not statistically significant. The effective refractory period of the right atrium was increased in nine patients and was unaltered in one patient. The mean increase was 26 ms ($p < 0{\cdot}005$). The effective refractory period of the right ventricle was increased in eight patients and unchanged in two patients. The mean increase was 18 ms ($p < 0{\cdot}005$).

Table 2 shows the changes in the accessory pathways. The effective refractory period in the anterograde direction, which was measured before and after bepridil administration in four patients, was increased in all four by an average of 45 ms ($p < 0{\cdot}02$). In another patient, all pre-excitation was abolished after bepridil administration. The

Myocardium (ms)					
	RA ERP			*RV ERP*	
PCL	*C*	*B*	*PCL*	*C*	*B*
500	220	260	500	210	220
500	210	220	500	210	210
500	190	190	500	190	210
500	220	230	600	230	250
00	200	220	500	220	220
400	190	200	400	240	260
600	200	250	500	220	260
400	180	210	350	175	190
500	210	240	600	220	240
00	200	260	400	210	240
	202 (13)	228 (24)		212 (19)	230 (24)
	<0·005			<0·005	

effective refractory period in the retrograde direction was increased in one patient by 60 ms and in another by 50 ms. The shortest cycle associated with 1:1 atrioventricular conduction by the abnormal pathway during rapid atrial pacing was measured in six patients with overt pre-excitation. After bepridil the cycle length was increased by an average of 40 ms ($p < 0{\cdot}005$).

During ventricular stimulation at increasing frequency, the shortest cycle length permitting 1:1 retrograde conduction by the abnormal pathway could be measured in eight patients before and after bepridil administration and increased in all patients (mean 43 ms, $p < 0{\cdot}001$).

In eight patients, reciprocating tachycardia could be induced by a single premature stimulus delivered during regular cardiac pacing (table 3). One patient only developed episodes of tachycardia in response to premature atrial or ventricular depolarisations provoked in sinus rhythm. In the remaining patient, induction of tachycardia required two ventricular extrastimuli delivered during pacing of the right ventricle. The zone of tachycardia was measured only in cases in which tachycardia was produced by a single extrastimulus elicited during regular pacing. In four patients a zone of tachycardia could be demonstrated by premature atrial stimulation before and after bepridil administration (table 3). The zone width increased in all four cases after bepridil (mean increase 60 ms). Two other patients showed a zone of tachycardia only after bepridil. On the other hand, in two other patients no sustained tachycardia was inducible by premature atrial stimulation after bepridil administration: only atrial echoes persisted, which in one patient were accompanied by non-propagated His bundle depolarisations. In five patients, a zone of tachycardia was obtained by premature ventricular stimulation before and after bepridil administration. After bepridil the zone width was increased in four of these patients by an average of 67 ms and unchanged in the fifth patient. In two other patients, the zone of tachycardia appeared after bepridil administration.

Tachycardia was recorded before and after

Table 2 *Effect of bepridil on accessory pathways (all values are ms)*

	Ante ERP AP			*Retro ERP AP*			*1:1 ante min PCL*		*1·1 retro min PCL*	
Case No	*PCL*	*C*	*B*	*PCL*	*C*	*B*	*C*	*B*	*C*	*B*
1	500	<220	<260	500	<220	<230	225	250	275	300
2				500	<220	<220			200	225
3	500	280	320	500	<190	<220	250	300	225	275
4	500	310		600	300	360	325		275	350
5	600	250	270	500	270	320	275	300	275	300
6				400	<250	<270			<300	350
7	500	<240	<260	500	270	<260	225	300	250	325
8	400	220	270	350	<185	<200	200	240	200	250
9				600	---				225	250
10	500	220	290	400	<220	270	225	250	225	<275
Mean (1 SD)		242 (29)	287 (24)		285 (21)	340 (28)	233 (26)	273 (29)	241 (33)	284 (42)
p value		<0 02					<0 005		<0·001	

Ante, anterograde conduction; retro, retrograde conduction; min PCL, minimum pacing cycle length. See footnote to table 1 for other abbreviations.

Table 3 *Effect of bepridil on atrioventricular reentrant tachycardias (all values are ms)*

	Initiation				
		Mode		*Zone of tachycardia*	
Case No	*PCL*	*C*	*B*	*C*	*B*
1	500	1VPB	1VPB	270–230	330–240
2	500	1APB	1APB	260–230	310–240
	500	1VPB	1VPB	250–220	320–280
3	500	1APB	1APB	290–200	320–220
	500		1VPB		300–220
4	500	1APB	1APB	310–240	510–260
	600	1VPB	1VPB	250–250	270–270
5	600		1APB		260–260
	500	1VPB	1VPB	250–250	340–230
6	400	1APB	1APB	270–260	310–290
7	500	2VPB	2VPB		
8	SR	1APB	2APB		
9	600	1APB		270–290	
	600	1VPB		320–290	
10	500	1APB		220–210	
Mean (1 SD)					
p value					

APB, atrial premature beat; VPB, ventricular premature beat, SR, sinus rhythm. See footnote to table 1 for other abbreviations.

bepridil administration in eight patients. In all cases the cycle length increased (mean 54 ms, $p < 0.005$) (table 3). The AH interval was increased in seven patients and reduced in one patient (mean increase 26 ms; NS). The HV interval was altered in only two patients (increased by 5 and 10 ms). The VA interval, related to retrograde conduction via the accessory pathway, showed an increase in five patients and no change in three others (mean increase 27 ms; NS).

Bepridil was well tolerated in all patients. The mean (1 SD) plasma concentration of the drug was 1·20 (0·39) mg/l.

Discussion

Previous clinical studies have shown that intravenous bepridil, in addition to reducing the sinus rate, prolongs the AH interval and the effective refractory period of the atrioventricular node[6-10] (changes consistent with blockade of the slow calcium channel). Furthermore, bepridil can depress intraventricular conduction and usually increases atrial and ventricular refractory periods. Because bepridil also has this effect on fast response tissues it would be expected to produce electrical changes in the atrioventricular aceessory pathways. The results of our study confirmed this prediction. Bepridil increased the refractoriness of the accessory pathways during both anterograde and retrograde conduction as was shown by the extrastimulus method and rapid cardiac pacing. Rowland *et al* recorded the clinical electrophysiological effects of bepridil (2 mg/kg intravenously) in 20 patients with atrioventricular reentrant tachycardia,[13] but they did not examine its effects on the accessory atrioventricular pathways. When Roy *et al* used intravenous bepridil (4 mg/kg) in four patients they found only an increase in the retrograde effective refractory period of the accessory pathway.[16]

The dual atrioventricular conduction pathways in patients with manifest-concealed pre-excitation accounts for the development of circus movement tachycardias.[20 21] In the most common variety the reentrant impulse is conducted in an anterograde fashion through the atrioventricular node and the bundle of His and returns to the atria via the accessory pathway. The antiarrhythmic activity of a drug may affect the factors initiating reentry—that is extrasystoles and/or the circuit itself in which the wave of tachycardia progresses.[22] The reported suppression of ventricular extrasystoles by bepridil[14] may therefore be beneficial in patients with accessory pathways. The depressant effect of bepridil on all parts of the atrioventricular reentry circuit should be useful in controlling reciprocal tachycardias. After bepridil two of the 10 patients in the present study no longer had electrically inducible tachycardia because they had conduction blocks within the atrioventricular node and the His-Purkinje system respectively. Often, however, there was an increase in the reentry zone. This paradoxical effect has also been seen with other drugs.[23] Antiarrhythmic action requires a critical balance between the changes in conduction velocity and the effective refractory period within the circuit. Without such a balance, qualitatively similar effects may favour the development of circus movement. Thus in this series bepridil caused electrophysiological *haracteristics*

R		*AH*		*HV*		*VA*	
	B	*C*	*B*	*C*	*B*	*C*	*B*
30	360	160	170	45	45	130	150
00	350	160	210	50	50	100	100
60	380	130	150	55	55	155	155
50	465	170	190	50	60	100	195
75	410	190	210	50	50	130	145
45	385	110	80	90	95	140	205
20	410	130	220	45	45	130	130
70	320	80	110	45	45	150	170
10		130		45		130	
0		60		55		170	
1 (34)	385 (44)	141 (36)	167 (51)	54 (15)	56 (17)	129 (20)	156 (34)
<0 005		>0 05		>0 10		>0 05	

changes that were clearly arrhythmogenic. Such responses to the drug have not been described previously. The clinical implications are unknown. Tachycardia during bepridil administration had a longer cycle length, an effect related to the depression of conduction in both the normal and accessory pathway. The role of bepridil in the treatment of supraventricular tachycardias remains unclear. Rowland *et al* reported that intravenous bepridil terminated reentry tachycardias associated with atrioventricular accessory pathways in half the cases.[13] The basis of this action was the development of an anterograde block in the atrioventricular node. There are no available data on the short term prevention of recurrences.

The results of the present study also indicate that bepridil may be useful in the treatment of atrial tachycardia of the Wolff-Parkinson-White syndrome. In this case, conduction via the accessory pathway is a possible source of life threatening high ventricular rates.[24] By increasing the anterograde effective refractory period of the accessory connection, bepridil may well slow down the ventricular response during atrial fibrillation. This is supported by recent findings on electrically induced episodes of atrial fibrillation.[16] In contrast, verapamil accelerated the ventricular response.[25] Furthermore, the prolongation of the atrial refractory period may have a role in the short term control of atrial arrhythmias.

Roy *et al* reported comparable electrophysiological effects on atrioventricular accessory pathways after oral bepridil.[16] The plasma concentration of the drug was not measured. The doses used (300–400 mg/day), however, give mean blood concentrations of 1–1·2 mg/l,[26]—that is in the range of the present study. Supraventricular tachycardia was prevented in five of the 11 patients on oral bepridil. Moreover, the results of repeat testing during oral treatment predicted the clinical outcome. Because ours was not a long term study we cannot draw definite conclusions about the predictive value of acute testing with intravenous bepridil.

The role of bepridil in patients with atrioventricular accessory pathways deserves further investigation. Additional information on the safety margin is required because several cases of torsade de pointes have been reported during bepridil treatment.[27] Studies now in progress in France aim at providing a precise answer to this question.

References

1 Canicave JC, Deu J, Jacq J, Paillet R. Un nouvel antiangoreux, le bepridil. Appréciation de son efficacité par l'épreuve d'effort au cours d'un essai à double insu contre placebo. *Thérapie* 1980;35:607–12.

2 Frishman WH, Charlap S, Farnham J, *et al* Combination propranolol and bepridil therapy in stable angina pectoris. *Am J Cardiol* 1985;55.43C–9C.

3 Di Bianco R, Katz RJ, Chesler E, Alpert JS, Spain JF. Long-term efficacy of bepridil in patients with chronic stable angina pectoris: results of a multicenter placebo controlled study of extended bepridil use. *Am J Cardiol* 1985;55:50C–4C.

4 Vogel S, Crampton R, Sperelakis N. Blockade of myocardial slow channels by bepridil (CERM 1978). *J Pharmacol Exp Ther* 1979,210:378–85.

5 Winslow E, Kane KA. Supraventricular antidysrhythmic and electrophysiological effects of bepridil, a new antianginal agent. *J Cardiovasc Pharmacol* 1981;3:655–67.

6 Ponsonnaille J, Citron B, Threil F, Heiligenstein D, Gras H. Etude des effets électrophysiologiques du bepridil utilisé par voie veineuse. *Arch Mal Coeur*

1982;75:1415–23.

7 Valere PE, Belin A, Chentir T, Lehner JP, Guerot C, Tricot R. Effets électrophysiologiques du bepridil sur le coeur humain. *Ann Cardiol Angeiol (Paris)* 1982;31:409–15.

8 Flammang D, Waynberger M, Hansen FH, Paillet R, Coumel P. Electrophysiological profile of bepridil, a new anti-anginal drug with calcium-blocking properties. *Eur Heart J* 1983;4:647–54.

9 Singh BN, Nademanee DK, Feld G, Piontek M, Schwab M. Comparative electrophysiologic profiles of calcium antagonists with particular reference to bepridil. *Am J Cardiol* 1985;55:14C–24C.

10 Upward JW, Daly K, Campbell S, Bergman G, Jewitt DE. Electrophysiologic hemodynamic and metabolic effects of intravenous bepridil hydrochloride. *Am J Cardiol* 1985;55:1589–95.

11 Fauchier JP, Cosnay P, Neel C, Rouesnel P, Bonnet P, Quilliet L. Traitement des tachycardies supraventriculaires et ventriculaires paroxystiques par le bepridil. *Arch Mal Coeur* 1985;78:612–8.

12 Levy S, Cointe R, Metge M, Faugere G, Valeix B, Gerard R. Bepridil for recurrent sustained ventricular tachycardias: assessment using electrophysiologic testing. *Am J Cardiol* 1984;54:579–81.

13 Rowland E, McKenna WJ, Krikler DM. Electrophysiologic and antiarrhythmic actions of bepridil. Comparison with verapamil and ajmaline for atrioventricular reentrant tachycardia. *Am J Cardiol* 1985;55:1513–9.

14 Kim SG, Fisher JD, Waspe LE, Matos J, Felder S. Reduction of ventricular arrhythmia by bepridil [Abstract]. *Circulation* 1985;72(suppl III):172.

15 McGovern BA. Efficacy of bepridil for ventricular tachycardia as determined by programmed cardiac stimulation. A multicenter study [Abstract]. *Circulation* 1985;72(suppl III):172.

16 Roy D, Montigny M, Klein GJ, Sharma AD, Cassidy D. Electrophysiologic effects and long term efficacy of bepridil for recurrent supraventricular tachycardia. *Am J Cardiol* 1987;59:89–92.

17 Scherlag BJ, Lau SH, Helfant RH, Berkowitz WD, Stein E, Damato AN. Catheter technique for recording His bundle activity in man. *Circulation* 1969;39:13–8.

18 Svenson RH, Miller HC, Gallagher JJ, Wallace RG. Electrophysiologic evaluation of the Wolff-Parkinson-White syndrome. Problems in assessing antegrade and retrograde conduction over the accessory pathway. *Circulation* 1975;52:552–62.

19 Wit AL, Weiss MB, Berkowitz WD, Rosen KM, Steiner C, Damato AN. Patterns of atrioventricular conduction in the human heart. *Circ Res* 1978;27:345–59.

20 Durrer D, Schoo L, Schuilenburg RM, Wellens HJJ. The role of premature beats in the initiation and termination of supraventricular tachycardia in the Wolff-Parkinson-White syndrome. *Circulation* 1967;36:644–62.

21 Gallagher JJ, Pritchett ELC, Sealy WC, Kasell J, Wallace AG. The preexcitation syndrome. *Prog Cardiovasc Dis* 1978;20:285–327.

22 Wellens HJJ. Effect of drugs on Wolff-Parkinson-White syndrome. In: Narula OS, ed. *Electrocardiography and clinical electrophysiology*. Philadelphia, Davis, 1975:367–85.

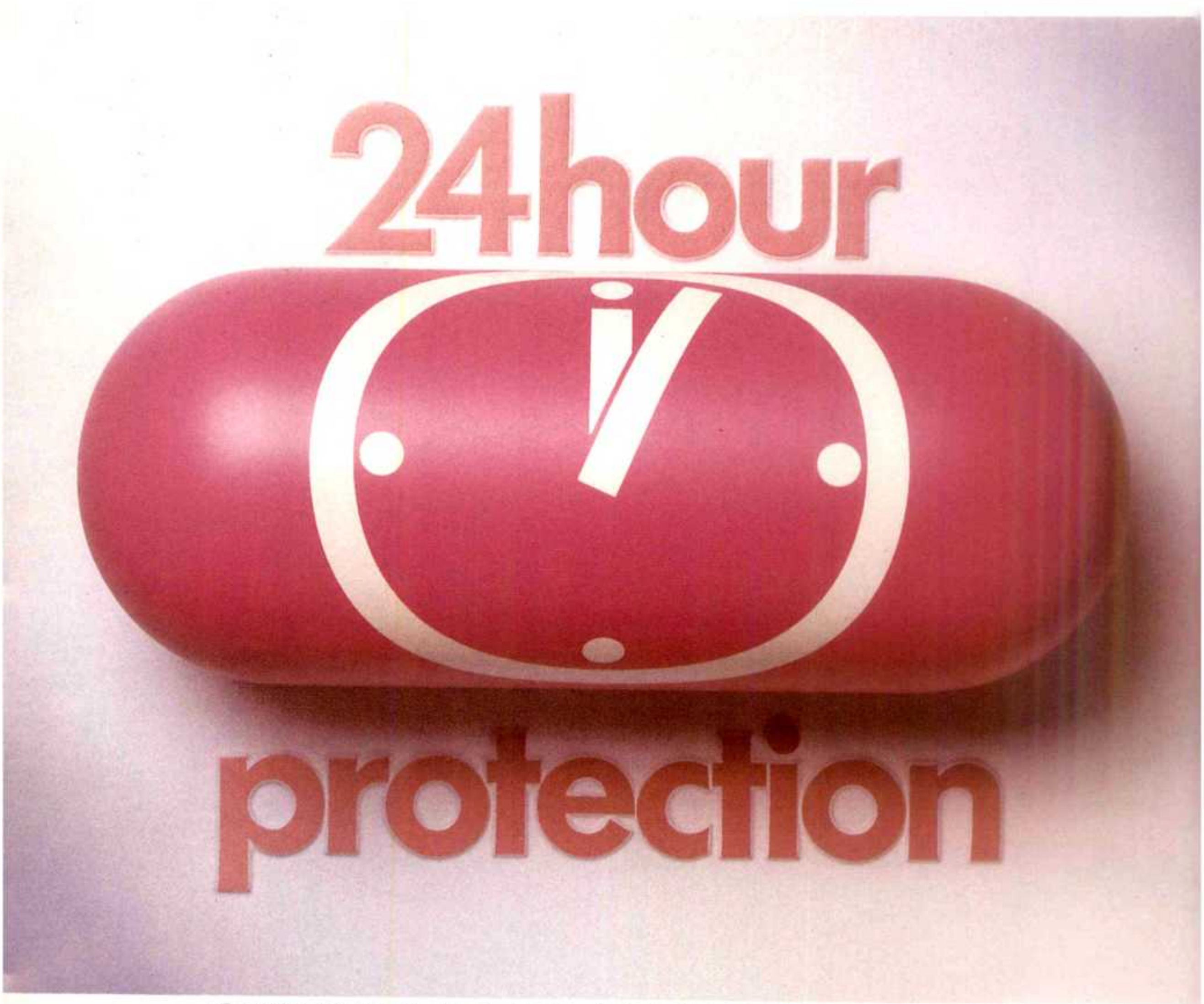
23 Kulbertus HE. The arrhythmogenic effects of antiarrhythmic agents. In: Befeler B, ed. *Selected topics in cardiac arrhythmias*. New York: Futura, 1980:113–9.

24 Campbell RWF, Smith RA, Gallagher JJ, Pritchett ELC, Wallace AG. Atrial fibrillation in the preexcitation syndrome. *Am J Cardiol* 1977;40:514–20.

25 Gulamhusein S, Ko P, Carruthers SG, Klein GJ. Acceleration of the ventricular response during atrial fibrillation in the Wolff-Parkinson-White syndrome after verapamil. *Circulation* 1982;65:348–54.

26 Benet LZ. Pharmacokinetics and metabolism of bepridil. *Am J Cardiol* 1985;55:8C–13C.

27 Leclercq JF, Kural S, Valere PE. Bepridil et torsades de pointes. *Arch Mal Coeur* 1983;76:341–8.



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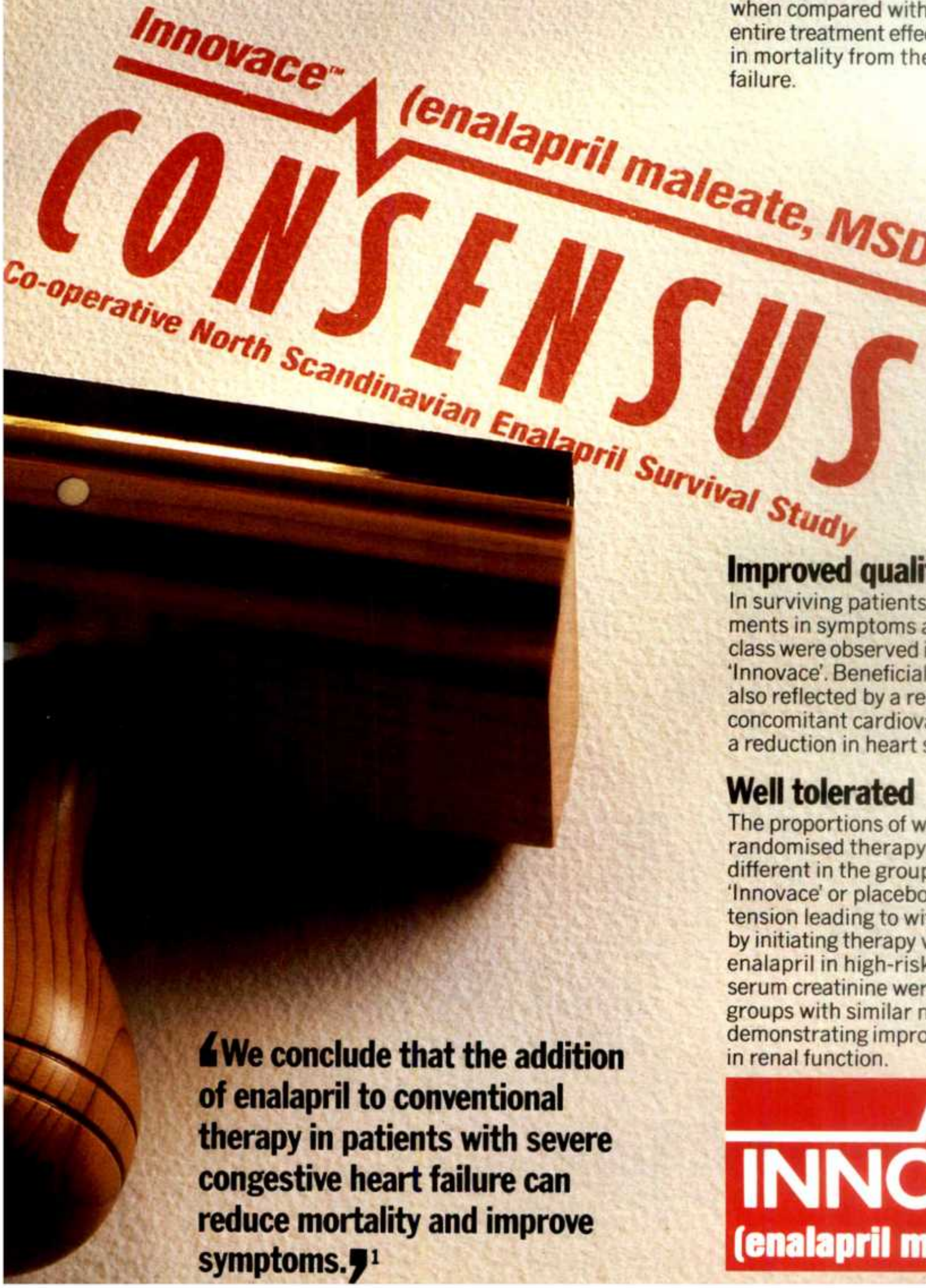
The CONSENSUS study[1] was set up in 1985 to evaluate the effect of enalapril ('Innovace'), given in addition to conventional therapy, on the prognosis of severe chronic heart failure. The results of the study were impressive – leading to the study being stopped prematurely by its Independent Ethical Review Committee.

Prolonged Survival

The reduction in mortality after six months was 40% in the group treated with 'Innovace' when compared with the placebo group. The entire treatment effect was due to a reduction in mortality from the progression of heart failure.



Improved quality of life

In surviving patients, significant improvements in symptoms and NYHA functional class were observed in the group treated with 'Innovace'. Beneficial treatment effects were also reflected by a reduction in the use of concomitant cardiovascular drugs and a reduction in heart size.

Well tolerated

The proportions of withdrawals from randomised therapy were not significantly different in the groups receiving either 'Innovace' or placebo. The incidence of hypotension leading to withdrawal was reduced by initiating therapy with a low dose of 2.5 mg enalapril in high-risk patients. Changes in serum creatinine were comparable in the two groups with similar numbers of patients demonstrating improvement or deterioration in renal function.

‘We conclude that the addition of enalapril to conventional therapy in patients with severe congestive heart failure can reduce mortality and improve symptoms.’[1]

INNOVACE™
(enalapril maleate, MSD)

1 9 8 7

Innovace™ (enalapril maleate, MSD)

CONSENSUS

Co-operative North Scandinavian Enalapril Survival Study

ABRIDGED PRODUCT INFORMATION

Full prescribing information is available and should be consulted before prescribing.

USES

All grades of essential hypertension and renovascular hypertension where standard therapy is ineffective or inappropriate because of adverse effects.

In congestive heart failure, as adjunctive therapy with digitalis and diuretics, treatment should always be initiated in hospital.

DOSAGE

Essential and renovascular hypertension: Therapy should be initiated with 5 mg in patients under 65 years of age; 2.5 mg if older or in presence of renal impairment. The usual maintenance dose is 10-20 mg once daily; maximum 40 mg once daily. When adding to a diuretic, the starting dose of 'Innovace' is 2.5 mg with the diuretic discontinued for 2-3 days prior to 'Innovace', if possible.

Reduce beta-blocker dose gradually after starting 'Innovace'. Dose titrate to BP requirements. Dosage of other antihypertensives may need adjusting.

Congestive heart failure: Can be used as adjunctive therapy with diuretics and, where appropriate, digitalis. Initial daily dose 2.5 mg under close supervision in hospital. If possible, diuretic dose should be reduced beforehand. Monitor blood pressure closely for hypotension.

Increase dose gradually to usual maintenance dose of 10-20 mg daily.

MODE OF ACTION

Following oral administration, 'Innovace' is rapidly absorbed and hydrolysed to enalaprilat, a highly specific, long-acting, non-sulphydryl angiotensin-converting enzyme inhibitor.

CONTRA-INDICATIONS

Pregnancy: assessment for possible pregnancy required if menstrual period is missed. Hypersensitivity.

PRECAUTIONS

Assess renal function prior to therapy with 'Innovace' and during treatment where appropriate. Should not be given with aortic stenosis or outflow tract obstruction.

Symptomatic hypotension is more likely following volume depletion caused by diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting or in patients with congestive heart failure with or without renal insufficiency. Severe hypotension reported mainly in patients with severe heart failure.

Impaired renal function: Caution should be used in patients with renal impairment. Renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Renal failure has been reported, mainly in patients with severe congestive heart failure or underlying renal disease, and is usually reversible. Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying artery stenosis. 'Innovace' is dialysable.

Renovascular hypertension: 'Innovace' can be used when surgery is not indicated or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases in blood urea and creatinine, reversible upon discontinuation of therapy, have been seen.

Because it is not known whether 'Innovace' is excreted in human milk, caution required if given to nursing mothers. Has not been studied in children.

Surgery/anaesthesia: 'Innovace' may lead to hypotension requiring volume expansion.

Drug interactions: Increased antihypertensive effect when combined with methyldopa, beta-blockers, calcium antagonists, or diuretics. Adrenergic-blocking drugs should be added with caution. Concomitant propranolol may reduce bioavailability. Lithium levels may be increased.

Plasma potassium usually remains within normal limits. 'Innovace' may elevate plasma potassium levels in patients with renal failure. Potassium supplements or potassium-sparing diuretics are not usually recommended, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. If deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

SIDE EFFECTS

Severe hypotension and renal failure.

Angioneurotic oedema has occurred rarely. Discontinue 'Innovace'; condition usually resolves without treatment, but give subcutaneous adrenaline (0.5 ml 1:1,000) if airways obstruction likely.

Most frequently, dizziness, and headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, urticaria, dysgeusia, and cough.

Clinical laboratory findings: Increased blood urea and plasma creatinine, decreases in haemoglobin, platelets, white cell count, and elevation of liver enzymes have occurred in a few patients, but causal relationship not established.

Overdosage: Hypotension most likely manifestation.

BASIC NHS COST

Tablets 20 mg: calendar packs of 28 tablets, £13.10; bottles of 50 tablets, £23.40. Tablets 10 mg: calendar packs of 28 tablets, £11.03; bottles of 50 tablets, £19.69. Tablets 5 mg: calendar packs of 28 tablets, £7.86; bottles of 50 tablets, £14.03. Tablets 2.5 mg: Bottles of 50 tablets, £10.

PRODUCT LICENCE NUMBERS

Tablets, 2.5 mg, 0025/0220; Tablets, 5 mg, 0025/0194; Tablets, 10 mg, 0025/0195; Tablets, 20 mg, 0025/0196.

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Issued August 1987

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Reference 1. The CONSENSUS Trial Study Group, *New Engl. J. Med.*, 1987, **316,** 1429-1435.

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A landmark study of enalapril in chronic heart failure

Br Heart J 1987;58:339–44

A comparison of bepridil with amiodarone in the treatment of established atrial fibrillation

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SUMMARY Fourteen patients with established atrial fibrillation (longer than three months) that was refractory to treatment were studied to compare the clinical and electrophysiological effects of amiodarone and bepridil. All patients initially received bepridil for three weeks (200–600 mg/day), followed by amiodarone for two to three months (100–400 mg/day). Bepridil seemed to be slightly more effective than amiodarone in converting the fibrillation to sinus rhythm (nine of fourteen compared with four of ten). The ventricular response in atrial fibrillation was equally well controlled by bepridil and amiodarone, both at rest and during exercise. Bepridil was associated with the development of ventricular arrhythmias in eight of fourteen patients; two had torsade de pointes, which in one degenerated into fatal ventricular fibrillation. These arrhythmias seemed to be associated with bepridil induced prolongation of the QTc interval. No ventricular arrhythmias were seen during amiodarone treatment.

Although bepridil seems to be an effective antiarrhythmic agent for the management of atrial fibrillation, its arrhythmogenic actions make it unsuitable for this purpose.

In chronic atrial fibrillation the usual therapeutic target is the slowing of the ventricular response, but a return to sinus rhythm may offer considerable additional benefits to the patient.[1] Most drugs used to suppress or prevent atrial fibrillation are inhibitors of the fast inward membrane current and tend to enhance atrioventricular conduction and are therefore usually given in combination with digoxin or other agents that slow conduction in the atrioventricular node. Amiodarone combines an antiarrhythmic effect in the atria with depression of atrioventricular conduction and is therefore useful in atrial fibrillation. As bepridil, introduced as an antianginal agent,[2 3] has been shown to have electrophysiological properties—blocking both the slow[4 5] and fast[6] inward currents and prolonging repolarisation—it might thus be expected to have similar actions to those of amiodarone. This study was designed to examine the antiarrhythmic potential of bepridil and compare its use in established atrial fibrillation with that of amiodarone.

Patients and methods

Fourteen patients with established atrial fibrillation of at least three months' duration and a ventricular rate of more than 100/minute were studied. The protocol was approved by the ethics committee of the Royal Postgraduate Medical School and all patients gave their informed and written consent.

Because of the long half life of amiodarone, randomisation of the order of drug administration was not practical. All antiarrhythmic medications were withdrawn for at least five half lives. Patients were then given bepridil for three weeks: 300 mg twice a day for two days then 100 mg twice a day for five days, increasing to 200 mg twice a day for the second week and 300 mg twice a day for the third week. In patients who remained in atrial fibrillation there was a two week wash-out period after bepridil was stopped and before amiodarone was started. Patients

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who reverted to sinus rhythm during bepridil were followed, off all antiarrhythmic medication, after stopping bepridil. If they reverted to atrial fibrillation amiodarone was introduced at least three weeks later. In all patients, amiodarone was administered in a loading dose of 800 mg/day for one week and then continued at 400 mg/day for two months. In those patients who converted to sinus rhythm on amiodarone, the daily dose was further reduced to 200 mg/day.

ASSESSMENT

Baseline rhythm and rate were assessed off medication immediately before bepridil, at the end of each week on bepridil, and after one and two months on amiodarone 400 mg/day. In those patients receiving the reduced dose of amiodarone a further assessment was made six to eight weeks later.

At each assessment a standard procedure was followed which required two outpatient visits on consecutive days. On the first day a two channel 24 hour ambulatory electrocardiogram (Oxford Medilog 1) was recorded. When the patient returned the following day, usually in the morning and always at the same time of day, blood was drawn for the measurement of the serum drug concentration (at least 12 hours after the last tablet) and a resting 12 lead electrocardiogram was recorded. At the same visit a symptom limited treadmill exercise test (Naughton protocol) was performed during which rhythm strips were recorded every three minutes and at peak exercise.

The predominant rhythm was determined from the resting 12 lead and ambulatory electrocardiograms. The ventricular rate was recorded during 10 second rhythm strips at rest and on peak exercise. If the patient was in sinus rhythm the QT interval was measured and the QT_c was derived (Bazett's formula).

The ambulatory electrocardiograms were analysed by a technician using a Reynolds Pathfinder II analysis system and checked by a physician. Rhythm variation was noted, as was the presence of ventricular arrhythmias.

Results

Table 1 shows the clinical data of the fourteen patients in the study.

In four patients bepridil was withdrawn early because of the development of arrhythmias. In one case ventricular bigeminy was present at rest, while in three patients non-sustained uniform ventricular tachycardia developed on exercise (tables 2 and 3).

Four patients did not go on to receive amiodarone. One patient died of a pulmonary embolus, a second died of torsade de pointes during the third week on bepridil, and two others did not complete the study.

CONVERSION TO SINUS RHYTHM

Nine of fourteen patients were converted to sinus rhythm during bepridil: two in the first week, four in the second week, and three in the third week. Atrial fibrillation reappeared in all nine patients within eight days of discontinuing bepridil.

Four of ten patients were converted to sinus rhythm during amiodarone (six of these had converted during bepridil (NS)): one by one month, two by two months, and one other after four months (maintenance dose 200 mg daily). Two of three patients remained in sinus rhythm when the amiodarone was reduced from 400 to 200 mg daily, while the third reverted to atrial fibrillation; sinus rhythm resumed when the dose was restored to 400 mg daily.

Neither the cause nor the duration of atrial fibrillation were related to the successful restoration of sinus rhythm during bepridil (table 1). During

Table 1 *Clinical details*

No	*Sex*	*Age*	*Diagnosis*	*Duration of AF*	*Bepridil*	*Amiodarone*
1	M	54	Pulm dis	Several years	+	+
2	M	62	DCM	Several years	+	+
3	F	61	L AF	3 mnth	+	−
4	M	62	L AF	1 yr	+	+
5	M	58	DCM	3 mnth	+	+
6	F	54	Rh VHD	Several years	+	+
7	F	73	Rh VHD	6 mnth	+	+
8	F	66	DCM	Several years	+	−
9	M	68	DCM	Several years	+	+
10	F	75	Rh VHD	Several years	+	−
11	F	65	Rh VHD	4 mnth	+	−
12	F	68	Rh VHD	1 yr	+	+
13	M	66	Rh VHD	4 mnth	+	+
14	M	60	L AF	3 mnth	+	+

AF, atrial fibrillation; Pulm dis, pulmonary disease; DCM, dilated cardiomyopathy; L AF, lone atrial fibrillation; Rh VHD, rheumatic valvar heart disease.

Table 2 *Rhythm during study*

	Bepridil			*Amiodarone*		
	Week			*Month*		
Patient	*1*	*2*	*3*	*1*	*2*	*3–4*
1	AF	AF	SR/AF	AF	SR	AF
2	AF	—	—	AF	AF	AF
3	AF	SR	SR Died			
4	AF	AF	AF	AF	AF	AF
5	SR	SR	SR	SR	SR	SR
6	AF	SR	—	AF	AF	AF
7	AF	AF	AF	AF	SR	SR
8	AF	SR	SR	—	—	—
9	SR	SR	SR	AF	AF	—
10	AF	AF	—	—	—	—
11	AF	AF	SR Died			
12	AF	AF	SR	AF	AF	AF
13	AF	SR	SR	AF	AF	SR
14	AF	AF	—	AF	AF	AF

AF, atrial fibrillation; SR, sinus rhythm; —, drug stopped.

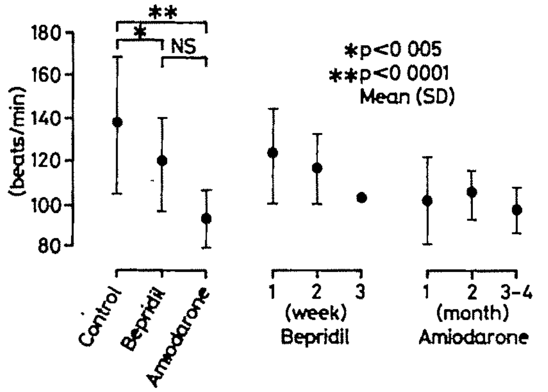

Fig 1 *Plot of maximal slowing of the ventricular response rate at rest on each drug and at each assessment point in those patients in atrial fibrillation.*

amiodarone treatment restoration of sinus rhythm was more common in patients with a shorter duration of atrial fibrillation.

CONTROL OF THE VENTRICULAR RESPONSE IN ATRIAL FIBRILLATION

Figures 1 and 2 show the ventricular rates at rest and during exercise respectively. During bepridil treatment there was progressive reduction in the rate over the three weeks; during amiodarone treatment maximal slowing was achieved at the first assessment at one month. Maximal slowing of the ventricular rate on the two agents was similar (figs 1 and 2, left hand panel).

REPOLARISATION AND VENTRICULAR ARRHYTHMIAS

At baseline assessments no ventricular arrhythmias were detected during 24 hour ambulatory electrocardiographic monitoring. However, they were documented in eight of fourteen patients during bepridil; two of whom developed torsade de pointes (table 3). Details of these two patients follow:

A 61 year old woman with lone atrial fibrillation reverted to sinus rhythm, albeit with paroxysmal atrial fibrillation, during the second week of bepridil. While undergoing routine ambulatory monitoring, she developed torsade de pointes; immediately beforehand she had been in sinus rhythm (QT_c 600 ms) with infrequent late-coupled ventricular extrasystoles, falling on the T wave (fig 3). The torsade de pointes promptly degenerated into ventricular fibrillation. Necropsy showed mild left ventricular hypertrophy of uncertain aetiology; there was no clinically significant coronary artery disease.

A 65 year old woman with rheumatic mitral valve disease also developed torsade de pointes. During the third week of bepridil treatment, the electrocardiogram showed atrial fibrillation with a rapid ventricular response and runs of broad complex tachycardia which were interpreted as aberration (fig 4, 25 October 1983); the QT interval could not be determined. The next day, she reverted to sinus rhythm with a pronounced bradycardia and a QT_c of 755 ms, with brief runs of non-sustained torsade de pointes. Bepridil was discontinued and no further episodes of torsade de pointes or other ventricular arrhythmias were documented. Amiodarone was not started because she died of a pulmonary embolism

Table 3 *Details of those patients who developed important ventricular arrhythmias while on bepridil*

Patient	*Week*	*Underlying rhythm*	*QT_c (ms)*	*Ventricular arrhythmia*
2	1	AF		VT on exercise, VT on Holter (26 episodes)
3	3	SR	600	Torsade de pointes degenerating into ventricular fibrillation
6	2	SR	560	Ventricular bigeminy on rest ECG
8	2	SR	490	Ventricular bigeminy on rest ECG; VT on Holter (1 episode)
10	2	AF		VT on exercise
11	3	AF		VT on rest ECG and on Holter (3 episodes)
	3	SR	755	Torsade de pointes on rest ECG
12	3	SR	524	Ventricular bigeminy on exercise and on Holter
14	2	AF		VT on exercise

VT, ventricular tachycardia, more than 3 complexes; Holter, 24 hour ambulatory ECG, AF, atrial fibrillation, SR, sinus rhythm.

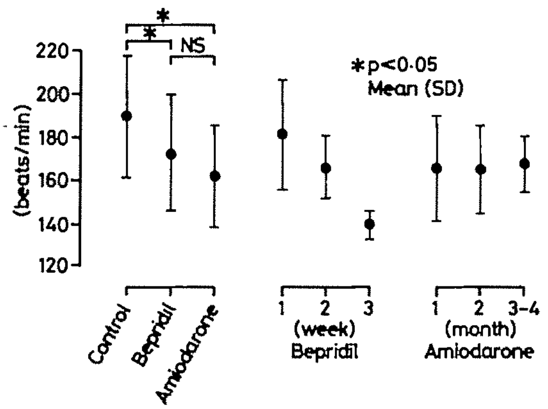

Fig 2 *Plot of maximal slowing of the ventricular response rate at peak exercise on each drug and at each assessment point in those patients in atrial fibrillation.*

five days after stopping bepridil, despite having been treated with anticoagulants.

Eight of the nine patients with sinus rhythm on bepridil had QT_c prolongation (greater than 440 ms) which was dose related (fig 5). Three developed ventricular arrhythmias, but five did not. The QT_c range in the former group was 524 to 755 ms (mean (SD) 586 (±103)) and in the latter group it was 408 to 521 ms (475 (±48)) (NS). Ventricular arrhythmias developed during sinus rhythm in five and during atrial fibrillation in four; in these latter the QT_c could not be derived. The two patients who developed torsade de pointes had conspicuous QT_c prolongation.

Discussion

When conversion to sinus rhythm is inappropriate, or unsuccessful, atrial fibrillation is managed by slowing the rapid ventricular response. Amiodarone not only slows atrioventricular nodal conduction, but also offers the potential extra benefit of conversion to sinus rhythm,[7] and there is thus an extra indication for considering its use in the management of atrial fibrillation.

Bepridil was introduced for angina[1 2] but has a wide electrophysiological profile, affecting both fast and slow inward channels. In the guinea pig ventricle the upstroke velocity is reduced,[4] while in the frog atria both slow and fast channel inhibition can be demonstrated.[8] In sheep muscle fibres and Purkinje fibres the upstroke velocity is reduced in asso-

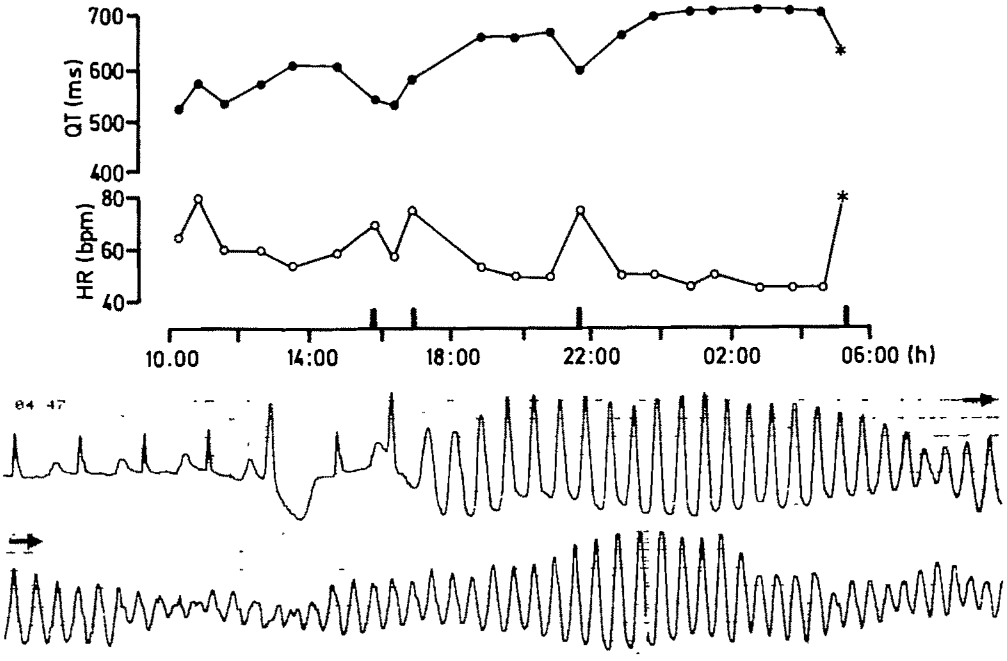

Fig 3 *Plot of heart rate and QT interval (taken from ambulatory electrocardiogram) in patient 3 on bepridil (300 mg twice a day). *Initiation of the episode of torsade de pointes and ventricular fibrillation, which is shown in the printout below.*

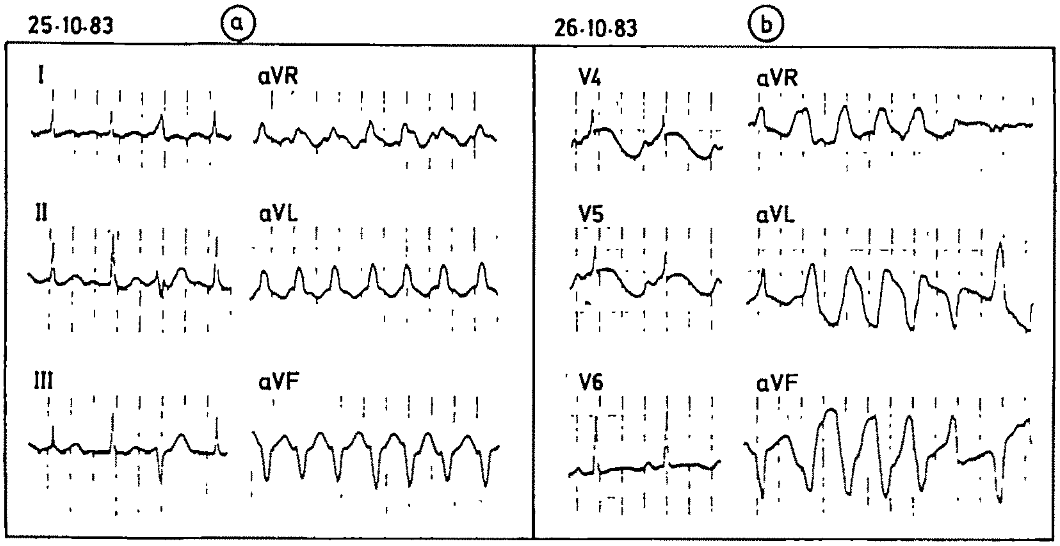

Fig 4 (a) Electrocardiogram obtained on 25 October 1983, in patient 11 showing atrial fibrillation with a rapid ventricular response (approximately 180/min). (b) Electrocardiogram on 26 October 1983 in patient 11 showing sinus rhythm (rate 95 beats/min) with considerable QT_c prolongation (755 ms). In leads aVR, aVL, and aVF there is a brief episode of torsade de pointes.

ciation with prolongation of the action potential duration in the muscle fibres and shortening of it in the Purkinje fibres.[6] It inhibits calcium flux in a similar manner to verapamil[4 5] and increases myocardial refractoriness in many tissues.[6] Studies of the electrophysiological effects of bepridil in man have shown that the increased myocardial refractoriness is most conspicuous in the atria.[7 9]

In previous studies amiodarone has been shown to convert approximately 50% of cases of atrial fibrillation to sinus rhythm, though the success rate is lower in cases of longer duration. Four of our ten patients who received amiodarone reverted to sinus rhythm, and six of the same ten patients were converted by bepridil; in the larger group of fourteen patients, nine reverted to sinus rhythm during the three weeks on bepridil—two in the first week, three in the second week, and four others in the third week. Thus bepridil seems to be at least as effective as amiodarone at inducing reversion.

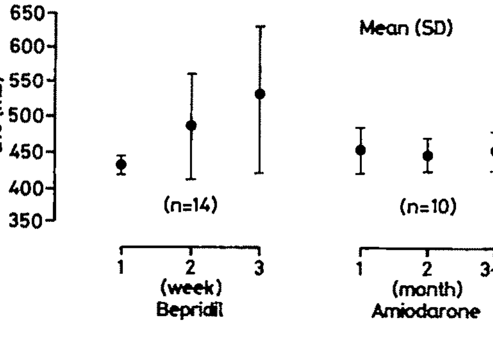

Fig 5 Plot of QT_c (mean (SD)) at each assessment point for those patients in sinus rhythm.

In those patients remaining in atrial fibrillation, the effects of the two agents on the atrioventricular node, both at rest and at exercise, were equal, and very similar to the effects of digoxin and verapamil.

While bepridil has effective antiarrythmic properties, it also has significant arrhythmogenic effects. Eight of the fourteen patients developed ventricular arrhythmias while on bepridil, in two instances torsade de pointes, which in one case degenerated into ventricular fibrillation. In a review of the French experience with bepridil there were sixteen cases of torsade de pointes.[10] All occurred in elderly women who had received bepridil 300 mg per day for over eight days. In fourteen the serum potassium was 4 mmol/l or less, but correction of this relative hypokalaemia did not abolish the torsade de pointes.

Bepridil has a long half life of over 50 hours, and the protracted recovery from torsade de pointes suggests that the relative hypokalaemia may not have been a major contributory factor.[10]

The two patients in this study who developed torsade de pointes had extremely long QT_c intervals, 600 and 750 ms. There was a direct relation between QT_c and daily dose of bepridil, which may explain the arrhythmogenic effect of bepridil. The relation between dose and the QT_c has not been examined in previous studies with bepridil, but there have been abnormalities of the T and U waves with prolongation of the QT interval.[3 11] In contrast, amiodarone was free of arrhythmogenic effects. The QT_c interval was prolonged but not to the same degree.

Therefore, in deciding whether bepridil offers a real advance, the benefits must be weighed against the potential risks. Bepridil is certainly a powerful antiarrhythmic agent that offers much for the management of atrial fibrillation. But the QT_c prolongation and arrhythmogenic effects are very worrying, particularly as the QT_c interval can only be derived with any confidence, if at all, once sinus rhythm has been achieved. In atrial fibrillation, the QT_c interval cannot be monitored as an early warning sign. Thus, in our opinion, the risks outweigh the benefits and bepridil does not offer an appreciable advantage over the established regimens or amiodarone.

References

1 Dreifus LS, Naito M, David D, Michelson EL. Atrial fibrillation: symptoms and haemodynamics. In: Kulbertus HE, Olsson SB, Schlepper M, eds. *Atrial fibrillation.* Mölndal, Sweden: AB Hässle, 1983:122–32.

2 Canicave JC, Deu J, Paillet R. Un nouvel antiangoreux, le bépridil. Appréciation de son efficacité par l'epreuve d'effort au cours d'un essai à double insu contre la placébo. *Thérapie* 1980;35:607–12.

3 DiBianco R, Alpert J, Katz RJ, *et al.* Bepridil for chronic stable angina pectoris: results of a prospective multicenter, placebo controlled, dose-ranging study in 77 patients. *Am J Cardiol* 1984;53:35–41.

4 Vogel S, Crampton R, Sperelakis N. Blockade of myocardial slow channels by bepridil (CERM-1978). *J Pharmacol Exp Ther* 1979;210:378–85.

5 Beaughard M, Ferrier M, Labrid C, Lamar JC, Leboeuf J, Piris P. Studies on bradycardia induced by bepridil. *Br J Pharmacol* 1982;75:293–300.

6 Kane KA, Winslow E. Antidysrhythmic and electrophysiological effects of a new antianginal agent, bepridil. *J Cardiovasc Pharmacol* 1980;2:193–203.

7 Rowland E, McKenna W, Holt D, Perelman MS, Krikler D. Oral amiodarone for the conversion of established atrial fibrillation [Abstract]. *Circulation* 1984;70(suppl II):II–439.

8 Labrid C, Grosset A, Dureng G, Mironneau J, Duchenne-Marullaz P. Some membrane interactions with bepridil, a new antianginal agent. *J Pharmacol Exp Ther* 1979;211:546–54.

9 Rowland E, McKenna WJ, Krikler DM. Electrophysiologic and antiarrhythmic actions of bepridil—comparison with verapamil and ajmaline for atrioventricular reentrant tachycardia. *Am J Cardiol* 1985;55:1513–9.

10 Leclerq JF, Kural S, Valère PE. Bépridil et torsades de pointes. *Arch Mal Coeur* 1983;76:341–8.

11 Dessoutter P, Haiat R. Modifications électrocardiographiques induites par le bépridil. *Arch Mal Coeur* 1980;73:1237–8.

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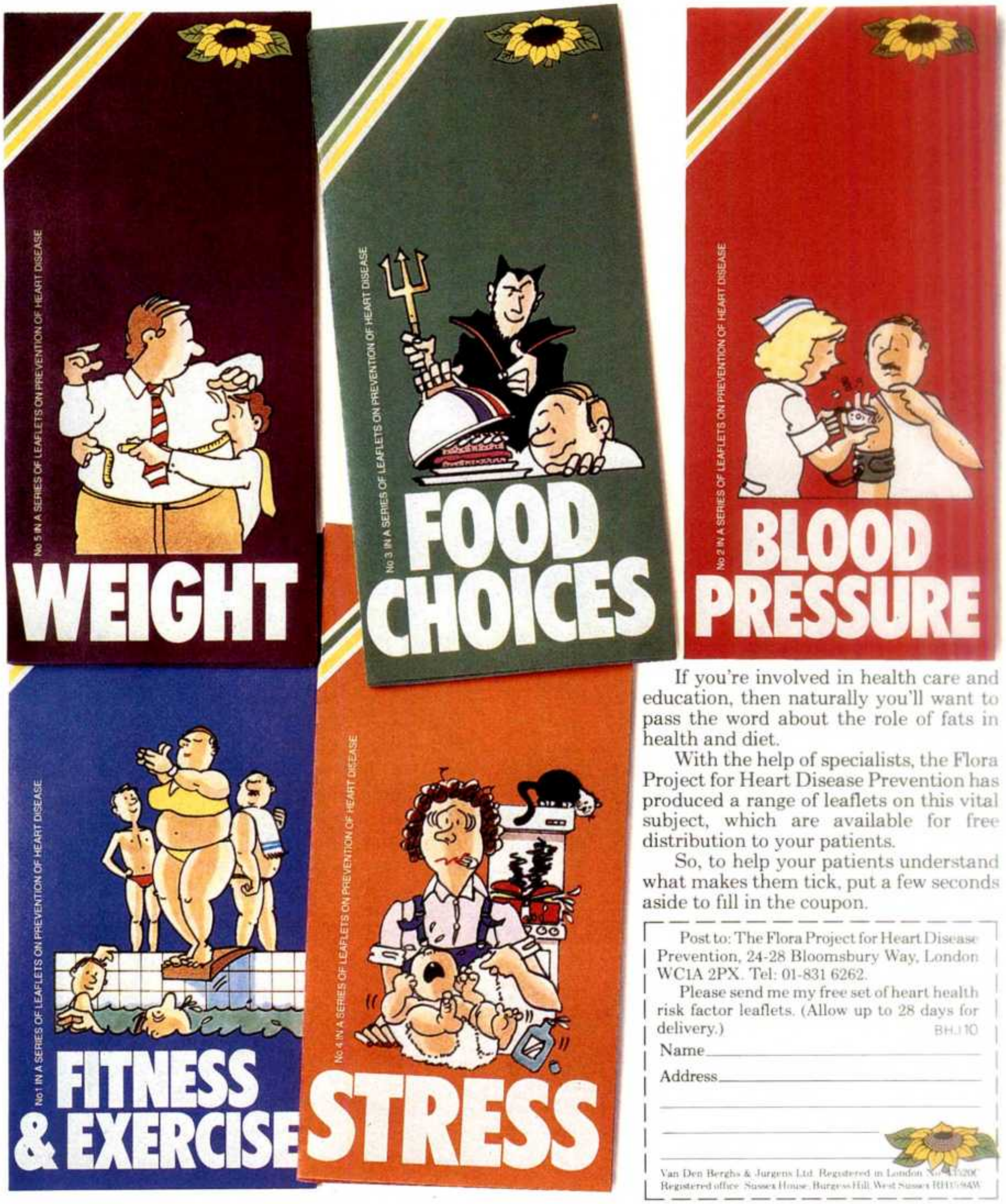
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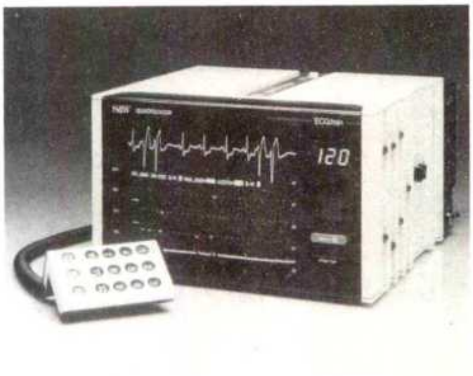

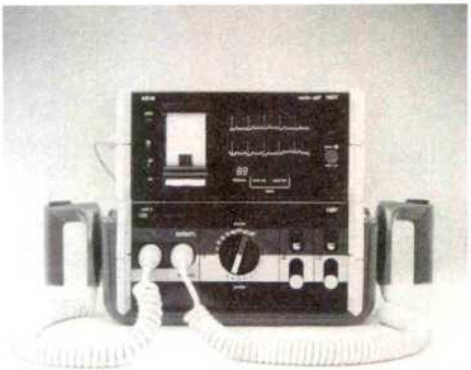

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Br Heart J 1987;58:345–51

The effects of early coronary patency on the evolution of myocardial infarction: a prospective arteriographic study

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SUMMARY The effects of early spontaneous coronary patency on the evolution of myocardial infarction were evaluated in 41 patients. They had coronary arteriography (mean (SEM)) 3·1 (0·2) hours after the onset of chest pain with repeat studies 90 minutes and three days later. In 12 (29%) patients the infarct related coronary artery was patent at the first arteriogram (group 1). A further 10 patients, nine of whom received thrombolytic treatment, showed early recanalisation of the infarct related coronary artery within 90 minutes of treatment (group 2). In the remainder the infarct related coronary artery was persistently occluded (group 3). Baseline values for infarct location, the sum of ST elevation in all leads, QRS scores, and serum creatine kinase activity did not permit discrimination between the groups. Nevertheless, patterns of ST segment change and enzyme release in group 1 were closely similar to those that occurred in response to thrombolysis in group 2. Thus compared with group 3, groups 1 and 2 showed earlier 50% reduction in the sum of peak ST elevation in all leads and earlier peaking of serum creatine kinase activity. Importantly, creatine kinase release was significantly attenuated in group 1, rising to a peak serum activity (mean (SEM)) of only 1242 (415) IU/l. Analysis of angiographic left ventricular ejection fractions at three days indicated limitation of infarct size in groups 1 and 2 compared with group 3. Mean (SEM) ejection fraction, however, was best preserved in group 1 (62 (6)%) and in this group the frequency of non-Q wave infarction was higher than in groups 2 and 3.

Thus in patients who present with a patent infarct related coronary artery early during infarction: (*a*) there is a reduction in the pattern of infarct size as reflected by attenuation of release of creatine kinase, preservation of left ventricular ejection fraction, and a relatively high frequency of non-Q wave infarction; (*b*) patterns of ST segment change and creatine kinase release resemble those that occur after successful thrombolytic treatment, suggesting that early coronary patency is the result of spontaneous recanalisation of a previously occluded artery.

The full transmural extent of myocardial infarction may not be established for six hours or more after thrombotic coronary artery occlusion.[1] Thus early recanalisation of the occluded coronary artery within this period may limit the ultimate extent of infarction by permitting reperfusion of the threatened myocardium.[2–4] This accounts for the beneficial effects of thrombolytic treatment on infarct size[5 6] and hospital survival[7–9] in patients treated early after the onset of symptoms. In a considerable proportion of cases, however, recanalisation occurs spontaneously either owing to unsustained spasm (spasm may be necessary for clot stabilisation) or to endogenous thrombolysis.[10] Nevertheless, the timing of spontaneous recanalisation is likely to be critical and the data of de Wood *et al* indicate that in many cases it occurs too late to permit clinically significant myocardial salvage.[10] Thus although a number of investigators have shown that patency of

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the infarct related coronary artery late after infarction is associated with more limited myocardial damage,[11-13] retrospective data of this type do not accurately identify the important subgroup in whom recanalisation occurs early enough to influence the evolution of infarction.

The present study is a prospective evaluation of patients with early patency of the infarct related coronary artery. Coronary anatomy was defined by arteriography during the acute phase of myocardial infarction. The effects of early coronary patency on the evolution of infarction were examined with particular reference to enzyme release, electrocardiographic changes, and infarct size.

Patients and methods

PATIENTS

Forty one patients (mean (SD) age 56 (9) years, 5 women and 36 men) were studied over a period of 18 months. All but one of these patients had been included in a randomised study of anisoylated plasminogen streptokinase activator complex, the results of which have been reported.[14] Patients with symptoms of acute myocardial infarction of less than six hours' duration were considered for entry. The site of the infarct was anterior in 21 cases and inferior in 20 cases. We studied only patients with ST segment elevation of $>0·1$ mV in one or more standard leads or $>0·2$ mV in one or more precordial leads that persisted despite treatment with nitrates. Exclusion criteria were a history of cerebrovascular accident, operation, or active peptic ulceration within the previous three months; severe hypertension ($>200/120$ mm Hg); or heart failure or external cardiac massage. All patients gave informed verbal consent for inclusion in the study which was approved by the hospital ethics committee.

STUDY DESIGN

After documentation of the degree of patency of the infarct related coronary artery by arteriography the patients were randomised to intravenous treatment. Twenty received anisoylated plasminogen streptokinase activator complex 30 mg and 20 received placebo. One patient was not randomised at the request of the referring physician. The degree of patency was reassessed by repeat coronary arteriography 90 minutes after treatment. Heparin sodium (1000 units/hour) was given by intravenous infusion four hours after catheterisation and was continued with dosage adjustments until completion of the final coronary arteriogram approximately three days later. During the study other drugs routinely used for the management of myocardial infarction were not withheld.

CORONARY ARTERIOGRAPHY

The first coronary arteriogram and the 90 minute follow up study were performed by modified Judkins' technique in a side room attached to the coronary care unit. Images were recorded on video tape. The three day coronary arteriogram (together with left ventricular angiography) was performed in the cardiac catheterisation laboratory with multiple projections recorded on cine film.

In one patient in whom a persistently occluded coronary artery was demonstrated equipment failure prevented recording of the acute phase coronary arteriograms on video tape. In a further four patients cardiac catheterisation at three days was not performed, because of clinical deterioration or death in three cases or the request of the referring physician in another one case. The remainder of the arteriographic recordings were complete and were reported by an independent cardiologist who is not an author of this paper. Patency was graded according to the criteria of the TIMI study group.[15] Recanalisation was defined as a change from TIMI grade 0 or 1 to 2 or 3. Left ventricular ejection fraction was calculated by hand digitisation of end systolic and end diastolic right anterior oblique angiographic frames with a microcomputer system (Commodore).

ELECTROCARDIOGRAPHIC AND ENZYMATIC DATA

A 12 lead electrocardiogram was recorded on admission, immediately before coronary arteriography, and again one, two, six, and 24 hours later. Recordings thereafter were performed every 24 hours for three days. All electrocardiograms were recorded at the standard calibration of 1 mV/cm at a paper speed of 25 mm/second. ST segment elevation was measured 0·04 seconds after the end of the QRS complex. The sum of the ST segment elevation in all leads ($\sum$ST) was calculated. The peak $\sum$ST elevation for each patient was defined as the maximum $\sum$ST elevation within six hours of the first coronary arteriogram. The electrocardiograms recorded at the time of hospital admission and at three days were scored according to the 29 point system described by Palmeri *et al*[16] on the basis of the Q and R wave duration and R to Q and R to S amplitude ratios. All electrocardiographic data were complete except for QRS scores at three days in the three patients who died.

Serum creatine kinase activity was measured on admission to the hospital and thereafter at every four hours for 36 hours. A final measurement was made at 48 hours. The upper reference limit for our laboratory is 200 IU/L. One patient (group 1) was excluded from the enzyme analysis because of severe but ultimately reversible rhabdomyolysis in the leg which complicated the acute catheter procedure. In the remaining patients 82% of the projected measurements were obtained.

STATISTICAL ANALYSIS

All averaged values are expressed as mean (SEM). The distribution of discrete variables between groups was compared by χ^2 testing. The median values between groups were compared by the Mann-Whitney test (non-parametric). Because there were three groups a total of only two comparisons was permitted. Those chosen were combined data for groups 1 and 2 versus 3 and the individual data for group 1 versus that for 2. ST segment and T wave changes were timed from the onset of chest pain. The rates at which ∑ST elevation resolved were compared on the basis of time from onset of chest pain to 50% of peak ∑ST elevation or to a ∑ST elevation of $\leqslant$0·3 mV or less, whichever occurred first.

Results

CORONARY ARTERIOGRAPHY: ACUTE FINDINGS

Coronary arteriography was performed 3·1 (0·2) hours after the onset of chest pain and was repeated 90 minutes later at 4·6 (0·2) hours. In none of the patients was there significant collateralisation of the infarct related coronary artery. Three subgroups were identified on the basis of the acute arteriographic findings. Group 1 was made up of 12 patients with TIMI grade 2 or 3 patency of the infarct related coronary artery at the first study. In each case, despite critical (>70%) luminal stenoses, the infarct related coronary artery remained patent at the follow up study. Group 2 was made up of 10 patients in whom the infarct related coronary artery was occluded at the first study with early recanalisation at the follow up study. Group 3 was made up of 19 patients in whom the infarct related coronary artery was occluded at the first study and in whom early recanalisation did not occur.

CORONARY ARTERIOGRAPHY: LATE FINDINGS

Approximately three days (65·6 (4·2) hours) after infarction, patency of the infarct related coronary artery was maintained in all group 1 patients, although only four had received anisoylated plasminogen streptokinase activator complex. In group 2 reocclusion occurred in one patient who had received anisoylated plasminogen streptokinase activator complex but patency was maintained in the remainder. In group 3 late recanalisation occurred in four patients, three of whom had received anisoylated plasminogen streptokinase activator complex.

BASELINE VARIABLES (Table)

There were no important differences between the groups in infarct location, history of previous infarction, or time from onset of chest pain to coronary arteriography. Baseline values for serum creatine kinase, ∑ST elevation, and QRS scores were also similar. Only the treatment randomisation showed significant differences. Thus 90% of group 2 received anisoylated plasminogen streptokinase activator complex compared with 33% and 37% of groups 1 and 3 respectively.

SERUM CREATINE PHOSPHOKINASE

Serial creatine kinase measurements during the 48 hours after hospital admission showed an increase to more than twice the upper reference limit in every patient except one (group 1). Peak values occurred significantly earlier in groups 1 and 2 than in group 3 (13·6 (1·5) versus 24·1 (1·1) hours, $p < 0{\cdot}01$) (fig 1). Although there was no significant difference in the time to peak serum concentrations between groups 1 and 2, creatine kinase release was significantly

Table *Baseline variables (mean (SEM))*

	Group 1 (Patent IRCA)	*Group 2 (Patent IRCA)*	*Group 3 (Occluded IRCA)*
Number of patients	12	10	19
History of previous infarction (n)	1	1	2
Infarct location (%):			
Anterior	58	60	42
Inferior	42	40	58
Anisoylated plasminogen streptokinase activator complex (%)	33	90	37
Coronary arteriography (hours after onset of chest pain)	3·2 (0·4)	2 8 (0 4)	3 3 (0 3)
∑ST elevation (mV)	1 4 (0 3)	1 7 (0 3)	1 2 (0 3)
Creatine kinase (IU/l)	265 (90)	165 (60)	148 (26)
QRS score	3 (1)	4 (1)	3 (1)

IRCA, infarct related coronary artery.
Conversion: traditional units to SI units—Creatine kinase: I IU/l = 16 7 × 10^{-3} μkat/l.

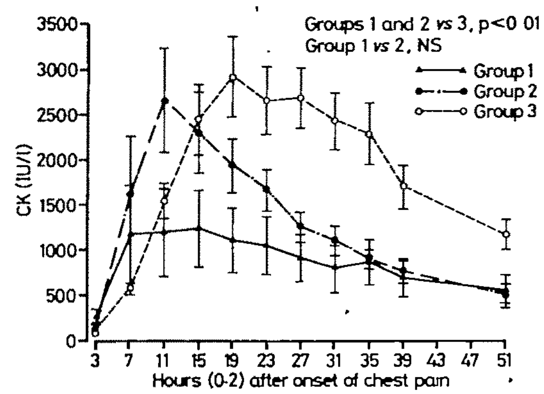

Fig 1 *Serum creatine kinase (CK) measurements during the 51 (0·2) hours after the onset of chest pain. Points and bars are mean values (SE) for groups 1 to 3.*

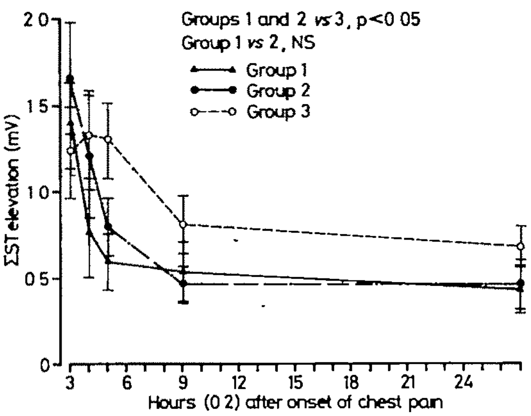

Fig 2 *∑ST elevation during the 27 (0·2) hours after the onset of chest pain. Points and bars are mean values (SE) for groups 1 to 3.*

attenuated in group 1, rising to a peak serum concentration of only 1242 (415) IU/l ($p < 0{\cdot}05$). Infarct location did not influence the enzymatic data.

ST SEGMENT CHANGES

Serial electrocardiogram recordings showed that ∑ST elevation was resolving during the first five hours after the onset of chest pain in groups 1 and 2 (fig 2). In group 3, on the other hand, resolution was delayed to between five and nine hours. Thus the time to 50% reduction in ∑ST elevation was significantly shorter in groups 1 and 2 than in group 3 (8·1 (1·7) versus 11·9 (2·4) hours, $p < 0{\cdot}01$). The difference between groups 1 and 2 was not significant. Infarct location did not influence the changes in ∑ST elevation.

INFARCT SIZE AT THREE DAYS

Angiographic left ventricular ejection fraction three days after admission was well preserved in groups 1 and 2 at 62 (6) and 56 (6)%, respectively (fig 3). In group 3 the left ventricular ejection fraction was significantly lower (45 (4)%; $p < 0{\cdot}05$). QRS scores showed a similar trend; however the differences between groups were not significant. Nevertheless, the frequency of non-Q wave infarction was significantly higher in group 1 than in groups 2 and 3 (42% versus 10% and 0%; $p < 0{\cdot}05$).

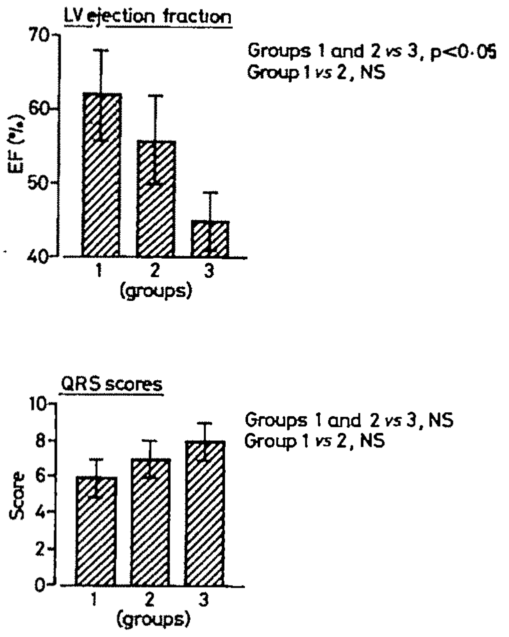

Fig 3 *Angiographic left ventricular (LV) ejection fraction and QRS score three days after admission. Mean values (SE) are shown for groups 1 to 3.*

Discussion

In this study coronary arteriography during the acute phase of myocardial infarction confirmed that a considerable proportion of patients have a patent infarct related coronary artery at the time of hospital admission. This is an important subgroup because, compared with patients in whom the infarct related coronary artery remains occluded, infarct size is reduced as judged by attenuation of creatine kinase release, a high frequency of non-Q wave infarction, and preservation of left ventricular ejection fraction at three days.

A simple non-invasive method for early identification of patients who present with a patent infarct related coronary artery would be of considerable clinical value, enabling the selection of specific treatment aimed at maintaining coronary patency. Our data, however, indicate that early identification is not possible on the basis of electrocardiographic and enzymatic criteria obtained at the time of presentation. Nevertheless, serial analysis of ST segment shifts and serum creatine kinase values shows a pattern of changes that has striking similarities to patients in whom thrombolytic treatment leads to early recanalisation of the infarct related coronary artery. In both groups ST segment elevation resolves more rapidly and serum creatine kinase peaks earlier than in patients with persistent occlusion of the infarct related coronary artery. Importantly, however, creatine kinase release is significantly attenuated in patients who present with a patent infarct related coronary artery, suggesting that myocardial damage may be less extensive in this subgroup.[17 18]

Further evidence for limitation of infarct size in patients with early patency of the infarct related coronary artery is provided by the data at three days. These show that patients of this type have a higher frequency of non-Q wave infarction,[19 20] and better preservation of left ventricular ejection fraction[21] than patients in whom the infarct related coronary artery is persistently occluded. Thus the mean value for ejection fraction in patients who presented with a patent infarct related coronary artery was greater than 60% despite a small preponderance of anterior infarcts within the subgroup, which might have been expected to bias the data towards more extensive myocardial damage.[21 22] Left ventricular ejection fraction was also well preserved in patients who showed early coronary recanalisation after thrombolytic treatment. Persistent occlusion of the infarct related coronary artery, on the other hand, was associated with significant depression of left ventricular ejection fraction at three days. These trends were to some extent reflected by the QRS scores, which tended to be lower in patients who presented with, or who developed, early patency of the infarct related coronary artery. Nevertheless, not all investigators have found a good correlation between QRS scores and left ventricular ejection fraction in patients with acute myocardial infarction[23-25]; this may explain why the differences between subgroups in the present study were not statistically significant.

Prospective arteriographic studies defining relations between early spontaneous coronary patency, enzyme release, electrocardiographic changes, and infarct size have not previously been reported. Ong *et al* inferred spontaneous coronary recanalisation in a subgroup of patients who showed early peaking of serum creatine kinase and improvement in radionuclide left ventricular ejection fraction.[26] The only available arteriographic studies, however, have been retrospective, based upon documentation of coronary patency late after myocardial infarction.[27-29] Studies of this type must be interpreted cautiously because in an indeterminate number of cases recanalisation will have occurred too late to exert an appreciable influence on the evolution of infarction. Nevertheless, the retrospective analysis reported by Hackworthy *et al*[27] shows some concordance with our own data. These workers found early peaking of serum creatine kinase activity and rapid resolution of ST segment elevation in patients later shown to have a patent infarct related coronary artery. When compared with patients in whom the infarct related coronary artery was occluded, however, the differences were less pronounced than in the present study and showed greater variability within subgroups. This is probably related to the inclusion of patients with late recanalisation within the subgroup with patency of the infarct related coronary artery. This may explain why these workers were not able to demonstrate significant differences in infarct size (as reflected by creatine kinase release and ejection fraction) between patients with and without patency of the infarct related coronary artery.

Our data demonstrated a significantly higher frequency of non-Q wave myocardial infarction in the patients who presented with a patent infarct related coronary artery (group 1). In two recent studies of non-Q wave myocardial infarction, the time to peak serum creatine kinase was shorter than in Q wave infarction and the frequency of patency of the infarct related coronary artery (demonstrated by predischarge arteriography at 11 (3) days) was higher.[28 29] De Wood *et al* have also demonstrated a high frequency (74%) of coronary patency in patients catheterised within 24 hours of the onset of symptoms who went on to evolve non-Q wave myocardial infarction.[30] Direct comparisons with our own data, however, are difficult because in only one of these studies was early ST segment elevation an inclusion criterion.[29] Nevertheless, the findings are in general agreement and have led to speculation that the pathogenesis of non-Q wave myocardial infarction may involve spontaneous coronary recanalisation. This certainly provides the most plausible mechanism for early coronary patency in the present study, unless infarction was the result of critical reductions of coronary flow without complete arterial occlusion. Thus every patient in group 1 presented with pronounced ST segment elevation suggesting recent coronary occlusion.[31] Moreover, the rapid resolution of ST segment elevation was closely similar to that which occurred in patients who had recanalisation after thrombolytic treatment. It is possible to speculate, therefore, that early coronary patency in group 1 was the result of endogenous thrombolysis occurring before coronary arteriography. Unsustained spasm may also have been a contributory factor, particularly since all patients in the study received nitrate treatment at admission to the hospital.

Acute myocardial infarction with early patency of the infarct related coronary artery is not uncommon. In the present series it was found in 29% of the patients, all of whom underwent coronary arteriography less than six hours after the onset of chest pain. Importantly, our data have demonstrated that within this subgroup with early coronary patency, myocardial damage is often relatively limited even when compared with patients treated successfully with thrombolytic agents. Indeed, although thrombolytic treatment is now recommended for coronary recanalisation in acute myocardial infarction, this may not be appropriate when the infarct related coronary artery is already patent. More work is required to define the mechanisms of myocardial infarction in this subgroup and to identify early non-invasive diagnostic criteria. Ultimately this may permit the development of specific treatment strategies directed at maintaining coronary patency and preventing progression to total coronary occlusion.

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References

1 Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979;**40**:633–44.

2 Maroko PR, Libby P, Ginks WR, *et al.* Coronary artery reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. *J Clin Invest* 1972;**51**:2717–23.

3 Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. I. Myocardial infarct size versus duration of coronary occlusion in dogs. *Circulation* 1977;**56**:786–94.

4 Baughman KL, Maroko PR, Vatner SF. Effects of coronary artery reperfusion on myocardial infarct size and survival in conscious dogs. *Circulation* 1981;**63**:317–23.

5 Smalling RW, Fuentes F, Mathews MW, *et al.* Sustained improvement in left ventricular function and mortality by intracoronary streptokinase administration during evolving myocardial infarction. *Circulation* 1983;**68**:131–8.

6 Simoons ML, Serruys PW, Van den Brand M, *et al.* Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. *J Am Coll Cardiol* 1986;**7**:729–42.

7 European Co-operative Study Group for Streptokinase Treatment in Acute Myocardial Infarction. Streptokinase in acute myocardial infarction. *N Engl J Med* 1979;**301**.797–802.

8 Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. *N Engl J Med* 1983;**309**:1477–82.

9 Gruppo Italiano per lo Studio della Streptochinasi nell' Infarcto (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;i:397–401.

10 De Wood MA, Spores J, Notske R, *et al.* Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;**303**:897–902.

11 Marmor A, Ludbrook PA, Sobel BE, Roberts R. Vascular determinants of early recurrent myocardial infarction [Abstract]. *Am J Cardiol* 1981;**47**·418.

12 Nygaard TW, Gibson RS, Craddock GB, Sirowatka J, Crampton RS, Beller GA. Comparison of patent and occluded infarct-related vessels at 2 weeks post-myocardial infarction in patients not receiving thrombolytic therapy [Abstract]. *J Am Coll Cardiol* 1983;**1**:579.

13 Hackworthy RA, Vogel MB, Harris PJ. Influence of infarct artery patency on the relation between initial ST segment elevation and final infarct size. *Br Heart J* 1986;**56**:222–5.

14 Timmis AD, Griffin B, Crick JCP, Sowton E. Anisoylated plasminogen streptokinase activator complex in acute myocardial infarction: a placebo controlled, arteriographic, coronary recanalization study. *J Am Coll Cardiol* 1987;**10**:205–10.

15 The TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial; phase I findings. *N Engl J Med* 1985;**312**:932–6

16 Palmeri ST, Harrison DG, Colele FR, *et al* A QRS scoring system for assessing left ventricular function after myocardial infarction. *N Engl J Med* 1982;**306**:4–9.

17 Shell WE, Kjekshus JK, Sobel BE. Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in creatine phosphokinase activity. *J Clin Invest* 1971;**50**:2614–25.

18 Bleifield WH, Hanrath P, Mathey D. Serial CPK determinations for evaluation of size and development of acute myocardial infarction. *Circulation* 1976;**53** (suppl I):108–11.

19 Spodick DH. Q-wave infarction versus S-T infarction. Nonspecificity of electrocardiographic criteria for differentiating transmural and nontransmural lesions. *Am J Cardiol* 1983;**51**:913–5.

20 Nicod P, Corbett JR, Sanford F, *et al.* Comparison of the influence of acute transmural and nontransmural myocardial infarction on ventricular function. *Am Heart J* 1984;**107**:28–34.

21 Shah BK, Pichler M, Berman DS, Singh BN, Swan HJ. Left ventricular ejection fraction determined by radionuclide ventriculography in early stages of first transmural myocardial infarction: relation to short-term prognosis. *Am J Cardiol* 1980;45:542–6.

22 Norris RM, Caughey DE, Deeming LW, Mercer CJ, Scott PJ. Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. *Lancet* 1970;ii:485–7.

23 De Pace NL, Iskandrian AS, Hakki A, Kane SA, Segal BL. Use of QRS scoring and thallium-201 scintigraphy to assess left ventricular function after myocardial infarction. *Am J Cardiol* 1982;50:1262–8.

24 Young SG, Abouantoun S, Savvides M, Madsden EB, Froelicher V. Limitations of electrocardiographic scoring systems for estimations of left ventricular function. *J Am Coll Cardiol* 1983;1:1479–88.

25 Fioretti P, Brower RW, Lazzeroni E, *et al.* Limitations of a QRS scoring system to assess left ventricular function and prognosis at hospital discharge after myocardial infarction. *Br Heart J* 1985;53:248–52.

26 Ong L, Reiser P, Coromilas J, Scherr L, Morrison J. Left ventricular function and rapid release of creatine for spontaneous reperfusion. *N Engl J Med* 1983, 309:1–6.

27 Hackworthy RA, Vogel MB, Harris PJ. Relationship between changes in ST segment elevation and patency of the infarct-related coronary artery in acute myocardial infarction. *Am Heart J* 1986;112:279–84.

28 Gibson RS, Beller GA, Gheorghiade M, *et al.* The prevalence and clinical significance of residual myocardial ischemia 2 weeks after uncomplicated non-Q wave infarction: a prospective natural history study. *Circulation* 1986;73:1186–98.

29 Huey BL, Gheorghiade M, Crampton RS, *et al.* Acute non-Q wave myocardial infarction associated with early ST segment elevation: evidence for spontaneous coronary reperfusion and implications for thrombolytic trials *J Am Coll Cardiol* 1987;9:18–25.

30 De Wood MA, Stifter WF, Simpson CS, *et al.* Coronary arteriographic findings soon after non-Q wave myocardial infarction. *N Engl J Med* 1986;315:417–23.

31 Pardee HEB. An electrocardiographic sign of coronary artery obstruction. *Arch Intern Med* 1920;26:244–57.

Br Heart J 1987;58:352–7

Left ventricular performance in alcoholic patients without chronic liver disease

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SUMMARY Left ventricular performance was studied non-invasively in 24 chronic alcoholics without liver disease. Twelve patients who had abstained from drinking for at least one month (group A) and 12 sex and age matched patients who had ceased drinking during the preceding 24 hours (group B) were studied at rest and during 50% submaximal exercise. Cardiac output and stroke volume were measured by first passage and left ventricular ejection fraction by multigated radionuclide cardiography. Twelve healthy sex and age matched controls were also studied. Haemodynamic variables were similar in group A and the controls, except that in group A left ventricular end systolic volume index did not decrease during exercise. In group B the heart rate was increased both at rest and during exercise and plasma noradrenaline concentrations were increased. The stroke volume index did not increase significantly during exercise in group B. In addition, the increase in left ventricular ejection fraction was smaller in group B than in controls. End systolic contraction was reduced in group B patients and diastolic blood pressure was increased.

These results suggest that cardiac abnormalities in chronic alcoholics may be reversed after cessation of drinking if no chronic liver disease is present. Recent alcohol consumption increases sympathetic nervous activity, impairs cardiac contractility, and increases afterload during physical stress.

Preclinical cardiomyopathy is frequently found in chronic alcoholics.[1-5] We have recently reported that determination of the left ventricular ejection fraction at rest and during exercise by radionuclide cardiography may be useful in the detection of subclinical cardiomyopathy in patients with alcoholic cirrhosis.[6] There was a slightly increased left atrial dimension but no significant alterations of systolic time intervals and echocardiographic variables at rest in cirrhotic patients who had ceased drinking compared with controls.[6] These findings indicated that at least some of the previously reported changes of cardiac function in chronic alcoholics[3-5 7-9] may be attributed to the influence of recent acute intoxication. This concept is supported by the study of Reeves *et al*, who found no echocardiographic evidence of cardiac dysfunction in alcoholics after prolonged abstinence.[10] In addition, the importance of chronic liver damage in the evolution of alcoholic cardiomyopathy has been a matter of debate,[11 12] the prevailing view being that overt cardiomyopathy is infrequent in cirrhotic patients.

The present study was undertaken (*a*) to characterise left ventricular function at rest and during exercise in chronic alcoholics *without* chronic liver disease, and (*b*) to evaluate the influence of recent

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Table 1 *Characteristics of patients and control subjects (medians with ranges in parentheses)*

	Group A	*Group B*	*Controls*
Age (years)	44 (37–59)	42 (28–63)	43 (30–56)
Sex (M/F)	9/3	9/3	9/3
Weight (kg)	69 (54–78)	67 (49–86)	76* (64–99)
Height (m)	1·73 (1·65–1·80)	1·73 (1·59–1·80)	1·79 (1·66–1·82)
Body surface (m^2)	1·82 (1·61–1·98)	1·80 (1·52–2·03)	1·94* (1·75–2·15)

*$p < 0·05$ *vs* patient groups

alcohol intake on left ventricular function in a similar group of patients.

Patients and methods

PATIENTS

All subjects gave their informed consent to the study, which was approved by the local ethics committee. We studied 24 patients attending the alcohol clinic of Frederiksberg Hospital. Exclusion criteria were evidence of chronic liver disease, cardiac disease (congenital, rheumatic, and ischaemic heart disease; cor pulmonale; and atrial fibrillation), hypertension, diabetes mellitus, anaemia, and endocrinological disorders. All patients had had a chronic alcohol intake of at least 100 g daily. Twelve patients (group A) with a history of 6–30 years (median 15 years) had abstained for a median period of 2 months (range 1–11). Twelve carefully matched patients (group B) with a history of 7–30 years (median 13 years) of alcoholism and abuse within the past 7 to 45 days (median 15 days) were investigated within 24 hours of their serum ethanol concentration falling to zero. All patients had started medical treatment with disulfiram, an abstention-supporting drug. Ten out of 12 patients in group B had received diazepam, an anxiolytic drug, to relieve symptoms of abstinence during the preceding 24 hours. In a few patients an additional dose of 5 or 10 mg was administered at least an hour before the haemodynamic investigation. Table 1 outlines patient characteristics and data from the sex and aged matched control group.

STUDY PROTOCOL

Venous blood samples were drawn for biochemical liver function tests and to rule out the presence of ethanol in serum. In patients with abnormal biochemical data the tests were repeated two weeks later to rule out chronic liver disease.

A bicycle exercise test was performed to determine the 50% submaximal work capacity of the subjects.

Radionuclide cardiography was performed with the patient upright at rest and during submaximal exercise corresponding to 50% of the maximal work capacity as determined by the exercise test. Autologous red blood cells were labelled in vitro with technetium-99m as previously described.[13] Cardiac output was determined by the first passage radionuclide technique.[14] A bolus of approximately 14 mCi (518 MBq) was injected into the right basilic vein and flushed with 20 ml of saline. The bolus passage was registered with a Siemens ZLC cardiac gamma camera equipped with a low energy all purpose parallel hole collimator in the left anterior oblique position with a 5 to 10° caudal tilt over the precordium. The first passage and equilibrium data were acquired by connecting the gamma camera to a Scintiview II nuclear medicine computer (Siemens). Stroke volume was determined as cardiac output divided by heart rate. The left ventricular ejection fraction was determined by multiple electrocardiogram-gated cardiography as described in detail elsewhere.[6] Left ventricular end diastolic volume was determined as stroke volume divided by left ventricular ejection fraction, and left ventricular end systolic volume as left ventricular end diastolic volume minus stroke volume.

Ascultatory blood pressure, heart rate, and plasma catecholamine concentrations were recorded during

Table 2 *Heart rate and blood pressure at rest and at submaximal workloads (medians with ranges in parentheses)*

	Group A		*Group B*		*Controls*	
	Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
Workload (W)	—	75 (65–100)	—	50* (25–85)	—	90 (60–140)
Heart rate (beats/min)	78 (62–100)	122 (100–140)	100* (70–130)	135* (120–145)	85 (63–100)	120 (95–133)
Systolic BP (mm Hg)	120 (110–140)	150 (130–170)	135 (105–180)	165 (130–195)	125 (110–145)	170 (120–205)
Diastolic BP (mm Hg)	85 (60– 90)	85 (75–100)	90 (80–110)	105† (85–115)	85 (75–95)	90 (70–105)

*$p < 0·05$ *vs* other groups. †$p < 0·05$ *vs* rest BP, blood pressure.

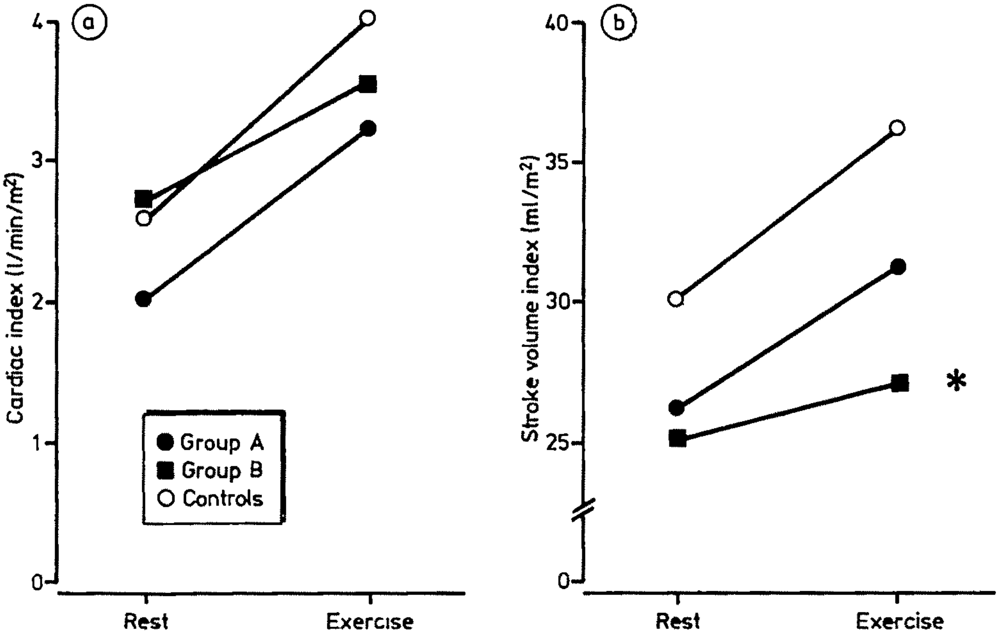

Fig 1 *Median values of (a) cardiac index and (b) stroke volume index at rest and during exercise in group A, group B, and controls.* $^*p < 0\cdot05$ *vs controls.*

the radionuclide data acquisitions. Plasma adrenaline and noradrenaline were measured by a single-isotope derivative assay.[15 16]

Data analyses were carried out by observers who were not aware of the group to which the patient belonged.

STATISTICAL ANALYSIS

Statistical analyses were carried out by the rank sum tests for paired (Pratt) and unpaired observations (Mann-Whitney). The results were expressed as median values and ranges. A p value $<0\cdot05$ was considered significant.

Results

The 50% submaximal workload in group A did not differ significantly from that in the control subjects, whereas the workload in group B was significantly reduced ($p < 0\cdot05$) (table 2). Heart rate was increased in group B both at rest and during exercise ($p < 0\cdot05$), but the heart rate changes in response to exercise were of the same magnitude in the three groups. There was an abnormal rise in diastolic blood pressure during exercise in group B (table 2).

Cardiac index tended to be lower in group A than in the controls ($0\cdot05 < p < 0\cdot10$). There were no significant differences between stroke volume index

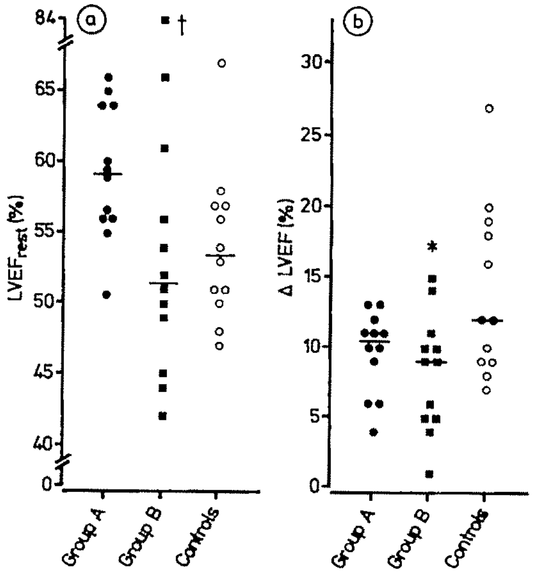

Fig 2 *(a) Left ventricular ejection fraction at rest* ($LVEF_{rest}$) *and (b) the increase in LVEF during exercise* (Δ LVEF). *Bars are median values.* $^\dagger p < 0\cdot05$ *vs group A;* $^*p < 0\cdot05$ *vs controls.*

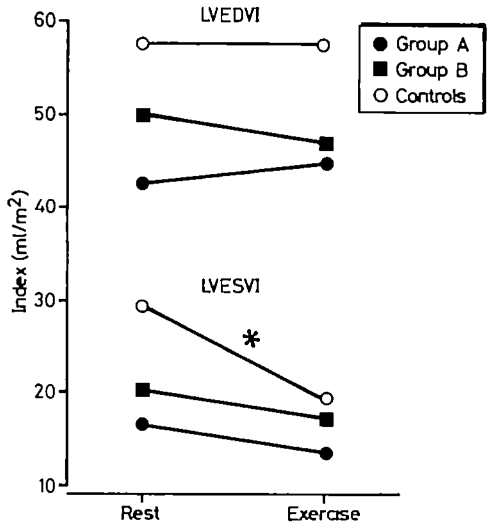

Fig 3 *Median values of left ventricular end diastolic volume index (LVEDVI) and left ventricular end systolic volume index (LVESVI) at rest and during exercise.*
**$p < 0{\cdot}05$ vs patient groups.*

at rest in the three groups. During exercise, however, stroke volume index was significantly lower in group B (median 27 ml/m^2) than in the controls (median 36 ml/m^2), $p < 0{\cdot}05$ (fig 1).

There was a wide range of results for left ventricular ejection fraction in groups A and B (fig 2). Left ventricular ejection fraction at rest was higher in group A than in group B ($p < 0{\cdot}05$). The increase in left ventricular ejection fraction from rest to exercise was 9% in group B and 12% in the controls ($p < 0{\cdot}05$) (fig 2).

Figure 3 shows the left ventricular volumes in the three groups. The left ventricular end diastolic volume index at rest was slightly lower in group A than in the controls, but this difference did not reach statistical significance ($0{\cdot}05 < p < 0{\cdot}10$). There were no significant changes in end diastolic volume from rest to exercise in any of the groups. The left ventricular end systolic volume index fell significantly in the controls but not in either group A or B (fig 3).

Plasma adrenaline concentrations at rest were similar in the three groups, and the increases in response to exercise were of the same magnitude (table 3). Plasma noradrenaline concentrations were not significantly different in group A and controls. In group B, however, plasma noradrenaline at rest was significantly higher than in group A or the controls ($p < 0{\cdot}05$). During exercise plasma noradrenaline concentrations were higher in group B than in group A (table 3).

Discussion

In the present study we measured central haemodynamic variables at rest and during submaximal exercise in patients with chronic alcohol abuse. Only seven patients had a history of alcohol abuse of < 10 years. In patients who had abstained from drinking for at least a month (group A) only three patients had an increase in left ventricular ejection fraction during exercise of <7%, suggesting that cardiac contractility was preserved in most patients of this group. In a previous study of patients with a comparable alcohol history we found left ventricular ejection fraction abnormalities in 12 out of 15 patients.[6] None of these patients were abusing alcohol at the time of investigation but all had biopsy-confirmed alcoholic cirrhosis. Comparison with the present results suggests that the development of chronic liver damage may have a role in the pathogenesis of alcoholic cardiomyopathy. This concept is supported by reports of severe cardiac failure developing in patients with alcoholic cirrhosis.[17] In another study it was reported that most of the hepatic changes found at necropsy of patients with alcoholic cardiomyopathy could be related to effects of acute and chronic congestive heart failure.[11] Ahmed *et al* evaluated cardiac haemodynamic function in alcoholic patients with and without cirrhosis and found that although overt cardiomyopathy was infrequent in cirrhotic patients, asymptomatic myocardial disease might become clinically important during volume or pressure overload.[12]

In our study the left ventricular end systolic volume index failed to decrease significantly during ex-

Table 3 *Plasma catecholamine concentrations at rest and during exercise (medians with ranges in parentheses)*

	Group A		*Group B*		*Controls*	
	Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
Adrenaline (ng/ml)	0·04 (0·02–0·20)	0·09 (0·04–0·38)	0·04 (0·00–0·07)	0·10 (0·03–0·15)	0·05 (0·01–0·10)	0·10 (0·03–0·18)
Noradrenaline (ng/ml)	0·51 (0·42–1·14)	0·72 (0·46–1·17)	0·74* (0·54–1·72)	1·07† (0·62–2·14)	0·55 (0·26–1·09)	0·91 (0·64–1·77)

*$p < 0{\cdot}05$ *vs* other groups. †$p < 0{\cdot}05$ *vs* group A. Conversion: traditional units to SI—adrenaline: 1 ng/ml = 5·46 nmol/l; noradrenaline: 1 ng/ml = 5·91 nmol/l.

ercise in both patient groups. In the face of a mean arterial blood pressure that was not higher than that in the control subjects, this result may be taken to indicate a reduction in cardiac contractility during physical stress, even in alcoholic patients without chronic liver disease.

The acute effects of alcohol intoxication on left ventricular performance have been thoroughly investigated in healthy subjects not consuming alcohol each day.[18–24] The results of these studies are conflicting, although the prevailing view is that intoxication depresses myocardial contractility. In two recent controlled non-invasive studies acute alcohol intoxication reduced stroke volume[25] and left ventricular ejection fraction.[26] In a study of cardiac performance in the hangover phase of acute alcohol intoxication heart rate, left ventricular ejection fraction, and cardiac output were increased.[27] Thus acute and recent intoxication would be expected to influence the results of haemodynamic investigations. Whereas patients of group A in our study were investigated at least one month after alcohol abstention, group B patients were examined within 24 hours after an alcohol excess. The two patient groups were matched in all respects except their drinking habit. Thus the differences in haemodynamic variables between group B and group A may be attributed entirely to recent alcohol intoxication in group B. Despite the reduced physical work capacity in group B, the workload applied to these patients was sufficient to produce an increase in heart rate similar to that in the other two study groups. Heart rate was increased both at rest and during exercise in group B, but otherwise there were no other haemodynamic alterations to indicate an increase in left ventricular performance. On the contrary, the lower left ventricular ejection fraction at rest, the small and insignificant increase in stroke volume from rest to exercise together with a reduced increase in left ventricular ejection fraction, and an insignificant decrease in left ventricular end systolic volume index suggest that cardiac contractility was impaired in alcoholic patients early after cessation of alcohol intake. The role of alcohol-induced hypertension in the development of alcoholic cardiomyopathy has been emphasised.[28] None of our patients had hypertension, but we cannot exclude the possibility that the abnormal rise in diastolic blood pressure during exercise in group B patients, which increased the afterload, may have contributed to the reduced left ventricular performance.[29]

Plasma catecholamine concentrations in group A did not differ from those in the control subjects, and no alterations were found in the plasma adrenaline concentrations in any of the patient groups. The increased plasma noradrenaline concentrations in group B were probably a result of the recent intoxication.[30] An increase in sympathetic nervous activity was also reflected by the increased heart rate. The concomitant increase in left ventricular performance in the early alcohol withdrawal phase described previously,[27] and recently supported by a study of healthy volunteers in our laboratory (unpublished data), however, could not be demonstrated in the alcoholic patients.

We examined left ventricular performance at rest and during 50% submaximal exercise in chronic alcoholics without liver disease. We found a reduced end systolic contraction during exercise in patients who had abstained from drinking for at least a month. In patients who had ceased drinking only within the past 24 hours sympathetic nervous activity was increased. Physical work capacity was reduced and left ventricular performance in response to exercise was abnormal. A reduced increase in stroke volume index and left ventricular ejection fraction reflected an impaired left ventricular contractility in the face of an increased afterload and despite an increase in sympathetic tone. Most of the changes in cardiac function in these patients will not be disclosed unless they are exposed to physical stress.

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References

1 Gould L, Shariff M, Zahir M, Dilieto M. Cardiac hemodynamics in alcoholic patients with chronic liver disease and a presystolic gallop. *J Clin Invest* 1969;48:860–8.

2 Zambrano SS, Mazzotta JF, Sherman D, Spodick DH. Cardiac dysfunction in unselected chronic alcoholic patients: noninvasive screening by systolic time intervals. *Am Heart J* 1974;87:318–20.

3 Mathews EC, Gardin JM, Henry WL, *et al.* Echocardiographic abnormalities in chronic alcoholics with and without overt congestive heart failure. *Am J Cardiol* 1981;47:570–8.

4 Kino M, Imamitchi H, Morigutchi M, Kawamura K, Takatsu T. Cardiovascular status in asymptomatic alcoholics, with reference to the level of ethanol consumption. *Br Heart J* 1981;46:545–51.

5 Dancy M, Bland JM, Leech G, Gaitonde MK, Maxwell JD. Preclinical left ventricular abnormalities in alcoholics are independent of nutritional status, cirrhosis, and cigarette smoking. *Lancet* 1985;i:1122–5.

6 Kelbæk H, Eriksen J, Brynjolf I, *et al.* Cardiac performance in patients with asymptomatic alcoholic cirrhosis of the liver. *Am J Cardiol* 1984;54:852–5.

7 Spodick DH, Pigott WM, Chirife R. Preclinical cardiac

malfunction in chronic alcoholism. *N Engl J Med* 1972;**287**:677–80.

8 Levi GF, Quadri A, Ratti S, Basagni M. Preclinical abnormality of left ventricular function in chronic alcoholics. *Br Heart J* 1977;**39**:35–7.

9 Askanas A, Udoshi M, Sadjadi SA. The heart in chronic alcoholism: a noninvasive study. *Am Heart J* 1980;**99**:9–16.

10 Reeves WC, Nanda NC, Gramiah R. Echocardiography in chronic alcoholics following prolonged periods of abstinence. *Am Heart J* 1978;**95**:578–83.

11 Lefkowitch JH, Fenoglio JJ. Liver disease in alcoholic cardiomyopathy: evidence against cirrhosis. *Hum Pathol* 1983;**14**:457–63.

12 Ahmed SS, Howard M, tenHove W, Leevy CM, Regan TJ. Cardiac function in alcoholics with cirrhosis: absence of overt cardiomyopathy—myth or fact? *J Am Coll Cardiol* 1984;**3**:696–702.

13 Kelbæk H, Gjørup T, Fogh J. In vivo stability of in vitro labelled ^{99m}Tc-red blood cells. *Nucl Med Commun* 1986;**7**:541–7.

14 Kelbæk H, Hartling OJ, Skagen K, Munck O, Henriksen O, Godtfredsen J. First passage radionuclide determination of cardiac output: an improved gamma camera method. *J Nucl Med* (in press).

15 Christensen NJ, Vestergaard P, Sørensen T, Rafaelsen OJ. Cerebrospinal fluid adrenaline and noradrenaline in depressed patients. *Acta Psychiatr Scand* 1980;**61**:178–82.

16 Kelbæk H, Gjørup T, Christensen NJ, Vestergaard B, Godtfredsen J. Cardiac function and plasma catecholamines during upright exercise in healthy young subjects. *Int J Cardiol* 1986;**10**:223–31.

17 Kelbæk H, Bødker B, Godtfredsen J. Congestive alcoholic cardiomyopathy. *Ugeskr Laeger* 1985; **147**:3472–4.

18 Regan TJ, Koroxenidis G, Moschos CB, Oldewurtel HA, Lenan PH, Hellems HK. The acute metabolic and hemodynamic responses of the left ventricle to ethanol. *J Clin Invest* 1966;**45**:270–80.

19 Riff DP, Jain AC, Doyle JT. Acute hemodynamic effects of ethanol on normal human volunteers. *Am Heart J* 1969;**78**:592–7.

20 Blomqvist G, Saltin B, Mitchell JH. Acute effects of ethanol ingestion on the response to submaximal and maximal exercise in man. *Circulation* 1970;**42**:463–70.

21 Newman WH, Valicenti JF. Ventricular function following acute alcohol administration: a strain-gauge analysis of depressed ventricular dynamics. *Am Heart J* 1971;**81**:61–8.

22 Ahmed SS, Levinson GE, Regan TJ. Depression of myocardial contractility with low doses of ethanol in normal man. *Circulation* 1973;**48**:378–85.

23 Horwitz LD, Atkins JM. Acute effects of ethanol on left ventricular performance. *Circulation* 1974; **49**:124–8.

24 Delgado CE, Fortuin NJ, Ross RS. Acute effects of low doses of alcohol on left ventricular function by echocardiography. *Circulation* 1975;**51**:535–40.

25 Kupari M. Acute cardiovascular effects of ethanol. A controlled non-invasive study. *Br Heart J* 1983;**49**:174–82.

26 Kelbæk H, Gjørup T, Brynjolf I, Christensen NJ, Godtfredsen J, Vestergaard B. Acute effects of alcohol on left ventricular function in healthy subjects at rest and during upright exercise. *Am J Cardiol* 1985;**55**:164–7.

27 Kupari M. Drunkenness, hangover, and the heart. *Acta Med Scand* 1983;**213**:84–90.

28 Friedman HS, Vasavada BC, Malec AM, Hasson KK, Shah A, Siddiqui S. Cardiac function in alcohol-associated systemic hypertension. *Am J Cardiol* 1986;**57**:227–31.

29 Lang RM, Borow KM, Neumann A, Feldman T. Adverse cardiac effects of acute alcohol ingestion in young adults. *Ann Intern Med* 1985;**102**:742–7.

30 Eisenhofer G, Lambie DG, Johnson RH. Effects of ethanol on plasma catecholamines and norepinephrine clearance. *Clin Pharmacol Ther* 1983;**34**:143–7.

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The aetiology and course of isolated severe aortic regurgitation: a clinical, pathological, and echocardiographic study

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SUMMARY Seventy two consecutive patients with severe isolated aortic regurgitation were evaluated by preoperative echocardiographic and angiographic assessment of the aortic root. Biopsy specimens of the aortic wall were taken at operation. Two major groups of patients were found: those with cusp derangement but normal aortic roots and those with normal cusps but dilated aortic roots. Of the 42 cases of abnormal cusps, 20 were rheumatic, 15 were infective, and six were bicuspid. One patient had a tear in an otherwise normal cusp. Of the 30 cases of abnormal roots but normal cusps, six had inflammatory changes (syphilis, Reiter's disease, giant cell aortitis) and 24 had root dilatation caused by non-inflammatory destruction of elastic laminae. Echocardiographic measurement of the aorta at the level of the top of the commissures predicted the findings at pathology. In 37 of 39 patients with cusp disease the measurement was <37 mm. In 27 of 33 patients with root disease the measurement was $\geqslant 37$ mm. This difference was statistically significant. There was no difference in the sizes of the prosthesis used in each group, suggesting that it was the diameter of the junction of the aorta with the sinuses rather than the junction of the sinuses with the ventricle that was important in aortic regurgitation.

Clinical progression in patients with non-inflammatory aortic root disease is slower than in patients with infective disease but faster than in those with rheumatic cusp disease.

Isolated aortic regurgitation has many known causes yet in a high proportion of patients who require valve replacement the exact aetiological diagnosis is uncertain. Because of this some clinical reports of patients with isolated aortic regurgitation have not distinguished between aetiological groups that may have different rates of progression.[1 2] In studies where aetiology was considered, it was unknown in 22–25% of the patients.[3 4] We have undertaken a prospective study in which the clinical course, preoperative echocardiograms of the aortic valve, and aortograms were correlated with studies of the cusps removed at operation and with biopsy specimens of the aortic root.

Patients and methods

We studied 72 (15 women aged 19–72 and 57 men aged 22–73) consecutive patients who had aortic valve replacement for isolated aortic regurgitation. Forty six patients were of British origin and 26 were foreign, mainly from the Middle East. All had symptoms: nine were in New York Heart Association class I, 18 in class II, 26 in class III, 15 in class IV, and four patients were operated on as emergencies because of rapidly worsening symptoms at rest. Dyspnoea was present in 94% of the patients, angina in 35%, and syncope or near syncope in 7%. Eighteen patients or 25% of the total had evidence of active or treated infective endocarditis.

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In assessing the progress of symptoms in different subsets of this cohort of patients the concept of a "break-point" was used.[4] This was the interval between the first appearance of symptoms and the time at which symptoms intensified to greater than New York Heart Association class II or required both digitalis and diuretics.

Preoperative electrocardiograms showed left ventricular hypertrophy in 85% of the study group and probable left ventricular hypertrophy in another 11%. The Romhilt-Estes criteria were used, and the mean (SD) score was 7·4 (2·4).[5]

M mode echocardiography was performed on all patients before operation.[6] The transducer was placed over the fourth left intercostal space; angulation of the transducer medially and cephalad permitted visualisation of the aortic root. The widest dimension that still kept the free edge of the cusps in view was recorded. Ultrasound frequency was 2·25 MHz. Aortic dimensions were measured by callipers initially, and these were subsequently verified by digitising the tracings with the Numonics Computer System.

Ninety two per cent (66/72) of the patients underwent cardiac catheterisation including aortography. Of those who did not have a catheter study, three were under 40 years of age making additional coronary artery disease unlikely. In the other three patients urgent surgery was indicated and catheter evaluation was thought inappropriate. In no patient was there another cardiac diagnosis sufficient in itself to warrant surgical intervention.

There was no pressure gradient between the left ventricle and the aorta on pull back tracings in 49 patients. Minor peak-to-peak gradients of five to 25 mm Hg were noted in 14 patients. Three patients with peak-to-peak gradients of 26–35 mm Hg were included because on clinical grounds the diagnosis was severe aortic regurgitation rather than aortic stenosis.

At operation, patients were given Hancock porcine heterograft valves (45), Starr Edwards (Model 1126U) ball and cage prostheses (12), or fresh nutrient homografts (15).

Biopsy specimens were taken 1 cm above the commissures from the edge of the aortotomy site and averaged 10 × 4 mm in size. Haematoxylin and eosin and Weigert-van Gieson's elastic tissue stains were used. The cusps were photographed before histology. The cusp area was measured by digitising the photographs. Echocardiographic and pathological examination were independent of any knowledge of the clinical findings.

The size of the lower border of the aortic annulus in each patient was assessed by the type and size of the prosthesis implanted. Patients in whom a homograft valve was inserted were excluded. Normal aortic valves were obtained from 35 necropsies on patients dying suddenly from non-cardiac causes and whose isolated left ventricular mass lay within the normal range for a subject with their total body mass. The aortic valve was fixed in the closed position by perfusion of the cross clamped aorta with formal saline at a hydrostatic pressure equivalent to 100 mm Hg.

Statistical analysis[7] included one-way analysis of variance to compare groups of patients.

Results

NORMAL VALVES

In normal aortic valves the total (mean (SD)) cusp area was 838 (139) mm^2 and bore a linear relation to the cross sectional area of the aortic root at commissural level ($r = 0·69$).

REGURGITANT VALVES

There were two groups of abnormal valves: those with a normal aortic root in whom abnormal cusps were responsible for the aortic regurgitation and those with an abnormal aortic root and basically normal cusps altered only by the secondary changes resulting from regurgitation.

Cusp disease was responsible for aortic regurgitation in 42 patients (58·3%) (table). In twenty (27·7%) the leaflets were shrunken, thickened, and retracted with reduction in the distance from base to the free edge (fig 1). This is typical of chronic rheumatic disease. The mean (SD) total cusp area was 575 (96) mm^2, significantly less than normal valve cusps ($p < 0·001$). Microscopical examination confirmed that the fibrosis had obliterated all normal cusp structure.

Fifteen patients with infective endocarditis had well defined perforations in the central area of the cusp associated in three instances with cusp

Table *Aetiology of aortic regurgitation in 72 cases*

Aetiology	*No*
Cusp disease:	
Rheumatic	20
Infective	15
Bicuspid	6
Torn cusp	1
Total	42 (58·3%)
Root disease:	
Non-inflammatory	24
Inflammatory	6
Syphilis (3)	
Reiter's disease (1)	
Ankylosing spondylitis (1)	
Giant cell aortitis (1)	
Total	30 (41·7%)

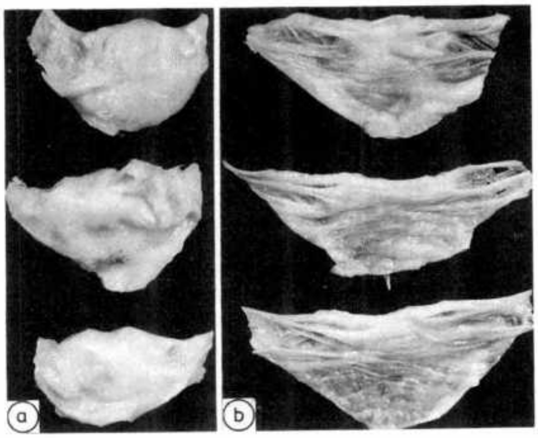

Fig 1 *Comparison of excised aortic cusps in rheumatic aortic incompetence (a) and aortic root disease (b). The cusps of rheumatic disease are smaller and thickened by fibrosis extending from the base to free edge. The cusps in root disease are larger and of normal thickness with only minimal fibrous thickening of the free edge.*

aneurysms. Nine of the infections were on bicuspid valves and six on tricuspid valves.

Six patients had non-infected bicuspid valves in which the leaflets were either strikingly unequal in size (fig 2) or had one leaflet with a deep notch in the free edge. One patient had a bicuspid valve with superimposed rheumatic heart disease and one patient had a spontaneous tear of a normal cusp.

Disease of the aortic root was present in 30 patients (table). Six of these were found to have inflammatory infiltration, usually in focal areas, associated with destruction of the aortic media. With the exception of one patient whose biopsy specimens included large numbers of giant cells, the chronic inflammatory response was non-specific. Clinical information allowed the diagnosis of syphilis in three of these patients, ankylosing spondylitis in one, and Reiter's disease in another.

In contrast, the remaining 24 of these 30 patients had non-inflammatory aortic root disease. Five of these 24 patients had coexistent bicuspid valves. The histological picture was that of patchy disruption and destruction of smooth muscle and elastic tissue in the aortic media. The degree of medial destruction varied, but all showed deposition of connective tissue mucins in areas of elastic fibre destruction (figs 3a–c). There was no inflammatory infiltrate within the media. The mean (SD) total cusp area in the patients with a tricuspid aortic valve was 942 (95) mm^2. The total aortic cusp area was higher than in normal hearts (mean 942 *vs* 838 mm^2 $p < 0{\cdot}025$). The cusps in these patients were thin, translucent, and pliable, and appeared normal in every way (fig 1). The only structural abnormality was an area of thickening caused by linear fibrosis on the free edge of the cusp. Histological examination did not show destruction or myxoid degeneration of the fibrous centre of the cusps. At the free edge, there was a knobbed fibrous thickening (fig 4).

ECHOCARDIOGRAPHY

All patients demonstrated left ventricular volume overload and diastolic fluttering of the anterior mitral leaflet or the septal endocardium and in some there was premature closure of the mitral valve.

The mean (SD) diameter of the aortic root at the level of the free edge of the aortic cusps in those patients subsequently found to have abnormal cusps was 32·1 (5·1) mm (fig 5). In patients with histopathological evidence of root disease the mean (SD) diameter was significantly larger ($p < 0{\cdot}001$) (42·3 (9·0) mm) (fig 6). Despite the difference in aortic root size, the diameter of the lower aortic ring or annulus as judged from the size of the prosthetic valves implanted was not different in the two groups (25·8 mm *vs* 26·3 mm).

The pathological findings in individual patients were predicted by the preoperative echocardiographic assessment of the valve. Thirty nine patients had root diameters at the commissural level of <37 mm. Of these, 37 (95%) were found at surgery to have normal aortic roots with the aortic regurgitation caused by cusp disease. Of those 33 patients with aortic root diameters $\geqslant 37$ mm, 28 (85%) were later found to have disease of the aortic wall accounting for the regurgitation. This difference is highly significant ($p < 0{\cdot}001$).

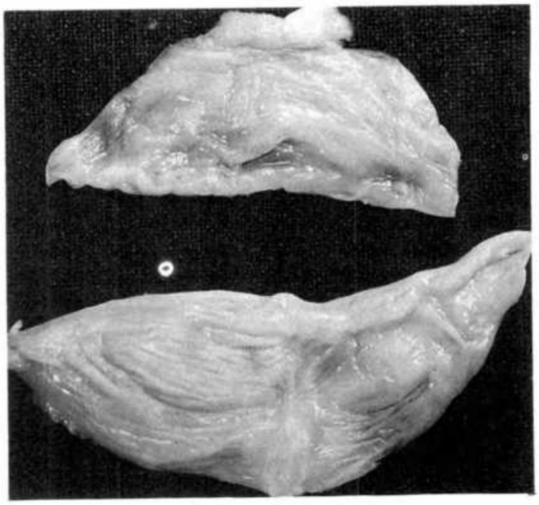

Fig 2 *Bicuspid aortic valve in which one cusp is larger and of a different shape than the other.*

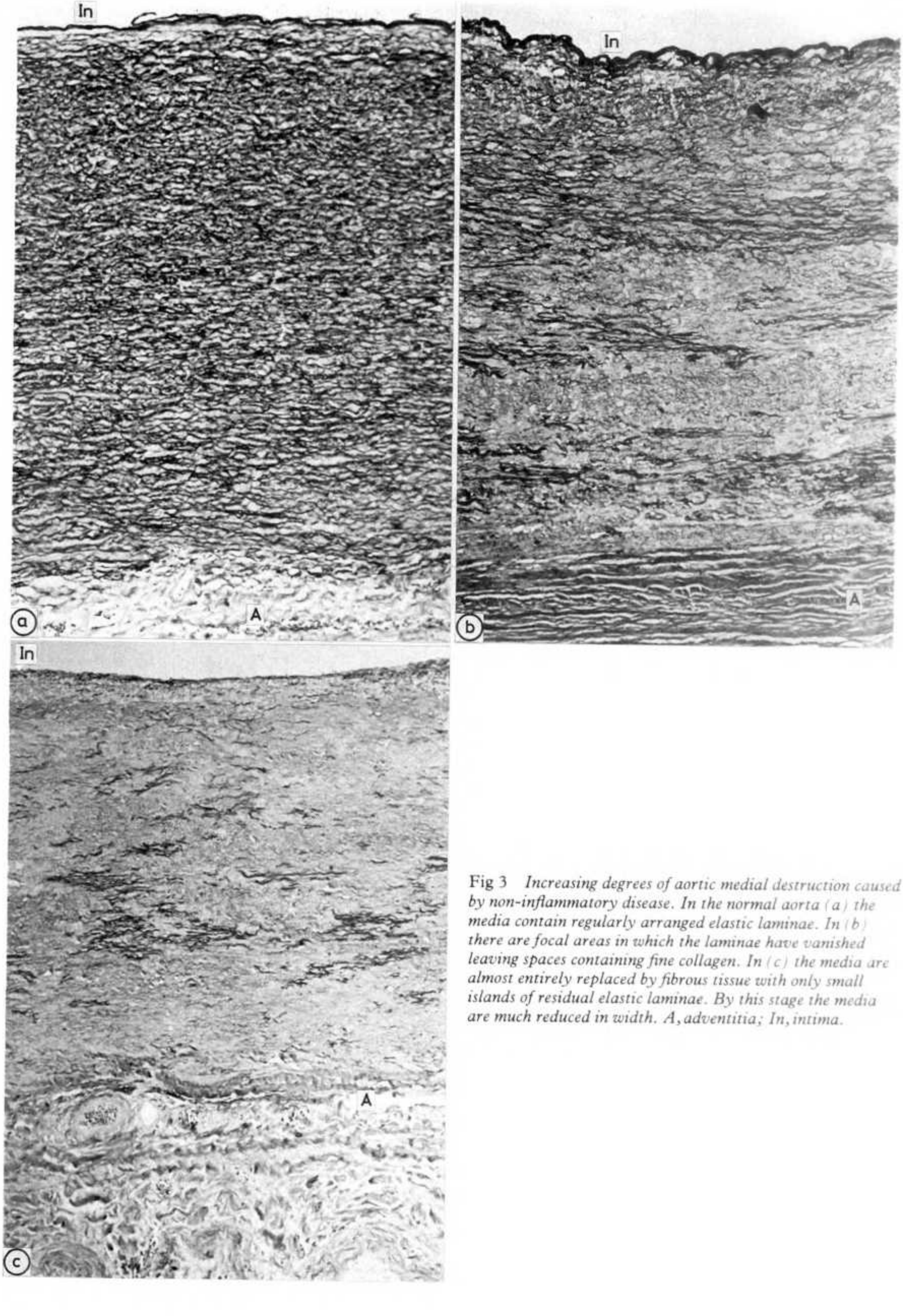

Fig 3 *Increasing degrees of aortic medial destruction caused by non-inflammatory disease. In the normal aorta (a) the media contain regularly arranged elastic laminae. In (b) there are focal areas in which the laminae have vanished leaving spaces containing fine collagen. In (c) the media are almost entirely replaced by fibrous tissue with only small islands of residual elastic laminae. By this stage the media are much reduced in width. A, adventitia; In, intima.*

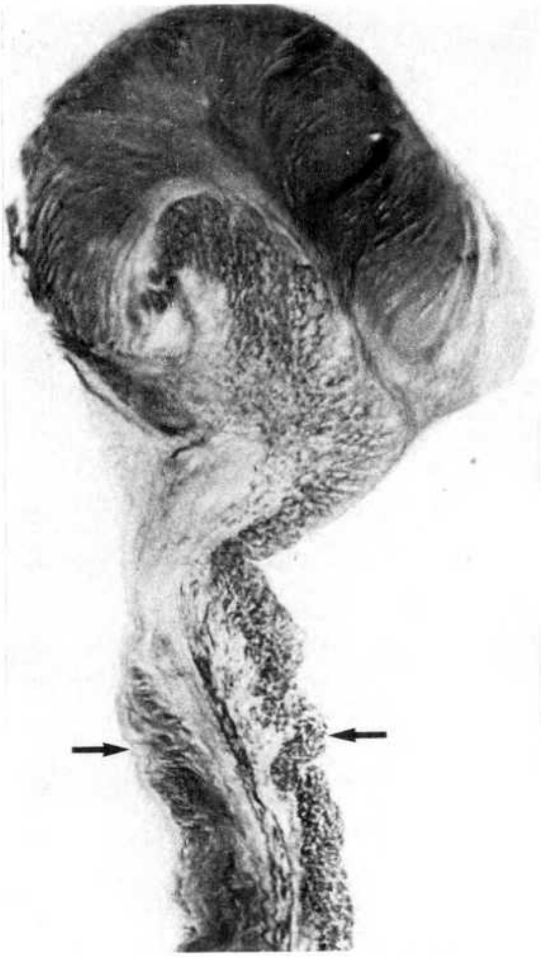

Fig 4 *Histological section across the cusp in aortic root disease. The body of the cusp (arrows) is of normal thickness and structure. The free edge has a round mass of collagen superimposed on the underlying structure. There are no vessels in the valve (elastic van Gieson stain, original magnification × 20).*

When 37 mm was used as the dividing line between normal and abnormal aortic roots, separation of the two groups is achieved with a sensitivity of 96·7%, a specificity of 88·1%, and a diagnostic accuracy of 91·6%.

The echocardiogram was also predictive of cusp pathology. In the patients with rheumatic disease the aortic leaflets were generally found to be thickened with heavy diastolic echoes (fig 5). The mitral valve apparatus was not found to be entirely normal on echocardiographic examination in any of these patients, even though in no case would mitral valve surgery have been contemplated. In patients with abnormal aortic roots the presence of a double echo from the free edge of the cusps (fig 6) was matched by finding fibrous thickening of the cusp edge in the operation specimen.

Eccentricity of the aortic valve closure line was seen in seven cases all of which had bicuspid valves. Thirteen patients without eccentric closure lines also had bicuspid valves, however.

ANGIOGRAPHY

Angiographic examination confirmed the clinical impression of severe aortic regurgitation. The degree of regurgitation was estimated by conventional criteria: width of the regurgitant jet, degree of opacification of the left ventricle, and rapidity of clearance of the dye from the left ventricle.[8]

The aortic root where cusp disease was responsible for the regurgitation was normal in size and marked by a definite waist just above the sinuses of Valsalva (fig 7). In cases in which aortic root abnormality was advanced, there was complete effacement of the aortic waist (fig 8).

PROGRESSION OF AORTIC REGURGITATION

Assessment of rate of progression of symptoms according to aetiological diagnosis showed that the course of disease differed in the three largest groups (fig 9). The mean (SD) course from the onset of symptoms to the break point was long in those with

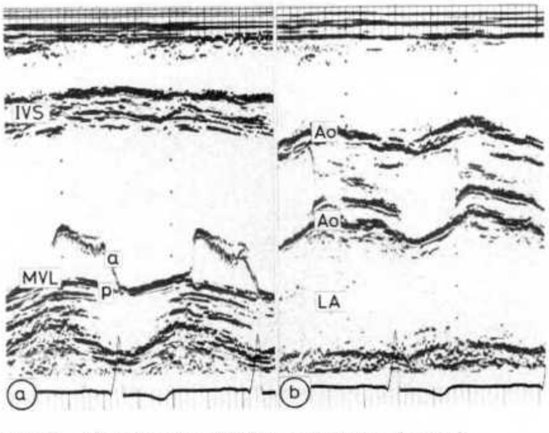

Fig 5 *M mode echocardiogram of rheumatic aortic regurgitation. (a) The mitral valve shows diastolic flutter of the anterior cusp and the posterior cusp is abnormal, indicating mild rheumatic disease. (b) The aortic root is not enlarged and the cusps are thickened.*

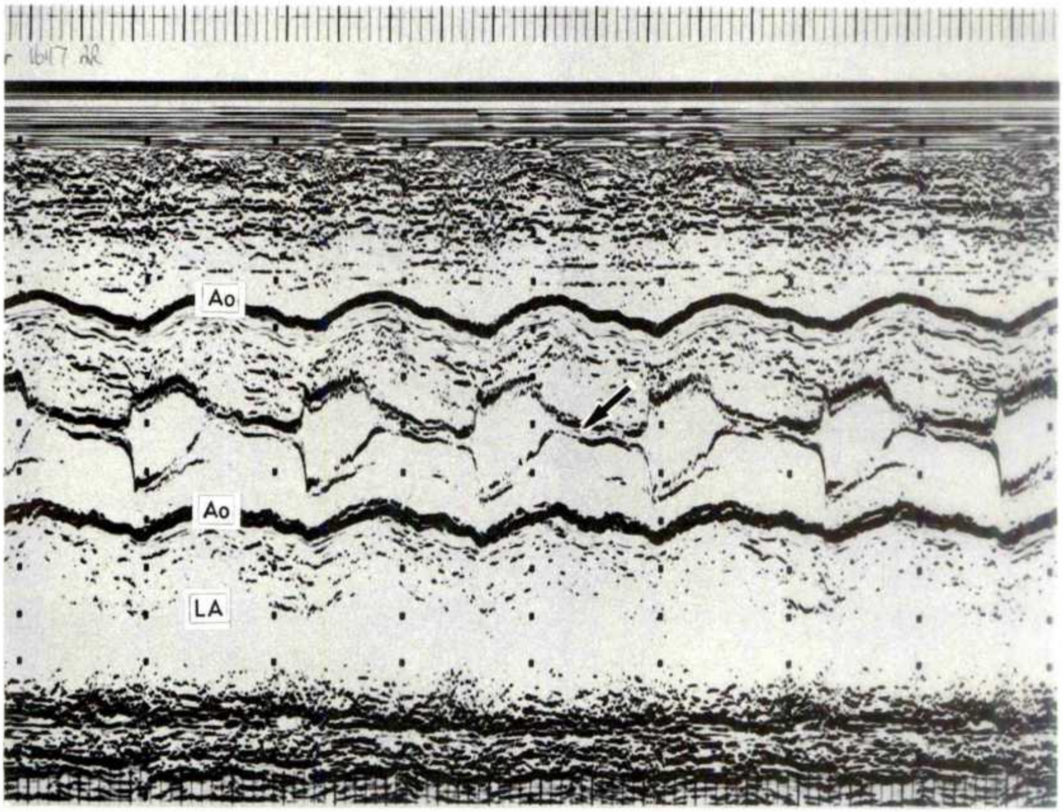

Fig 6 *M mode echocardiogram of aortic regurgitation caused by a dilated aortic root. The diameter of the aorta at commissural level is 4·3 cm. The free edges of the cusps produce a double echo (arrow).*

rheumatic disease (82·6 (68) months) and short in those with infective endocarditis, either controlled or uncontrolled (10·1 (19) months. In those with non-inflammatory aortic root disease there was an intermediate course (20·6 (24·3) months). These differences are highly significant ($p < 0{\cdot}001$).

Discussion

An understanding of the pathophysiological mechanisms of aortic regurgitation requires a review of the normal anatomy and function of the valve. For such a purpose normal aortic valves were fixed in the closed position under a hydrostatic pressure equivalent to 100 mm Hg. This provided for distension of the sinuses of Valsalva to a degree approximating their position in life (fig 10). When thus examined, the aortic root was seen to consist of a sleeve of about 1·5 cm in length bounded by ring-like structures both above and below with a distended area, the sinuses, in between. The lower ring, which lies below the cusps (fig 11) and forms the attachment of the aorta to the left ventricle, is made up in part by the myocardium of the upper interventricular septum and in part by the base of the anterior leaflet of the mitral valve. Its fibrous support structure can be dissected out as part of the so-called cardiac skeleton and is familiarly, but perhaps misleadingly, known as the aortic annulus. The upper border of the aortic sleeve forms another definite circular ring at the level of the attachment of the aortic commissures and forms a major part of the structural support for the cusps. This has been termed the supra-aortic ridge or sinotubular junction. The cusps are contained within the aortic sleeve and meet at the commissures which are attached to the supra-aortic ridge. Just above the sleeve with its enclosed cusps, the more familiar smooth muscle layers and elastic laminae of the wall of the tubular portion of the ascending aorta merge with the more collagenous connective tissue of the sleeve. The tissue of the aortic sleeve bulges outward in life more than the elastic

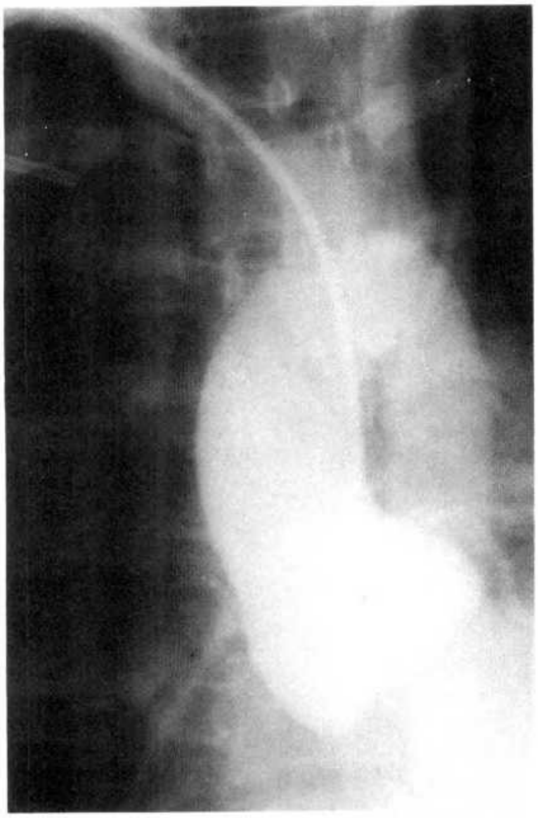

Fig 7 *Aortic regurgitation caused by gross dilatation of the aortic root with normal leaflets.*

containing aorta and forms the sinuses of Valsalva.

Examination of the closed aortic valve from above reveals that cusp support depends on two factors, the firm fixation of the cusps to the supra-aortic ridge at the commissures and the abutting of the ventricular surfaces of adjacent cusps. Examination of the ventricular face of the cusps shows a central nodule or corpus Arantii from which ridges extend to the fixed edges of the cusp where it merges with the wall of the aortic sleeve. This ridge forms the true line of closure or apposition of each cusp as it abuts its neighbour. Above the line of closure, a more filamentous area of each cusp (lunula) provides a measure of overlap with a similar portion of the abutting cusp. The free edge of each cusp at the outer edge of this filamentous area acts like a guy-rope supporting the cusp in diastole. In older patients, fenestrations are commonly noted in the lunulae; these have no functional importance since the communication is only between aortic sinuses above the line of closure. The linear relation between aortic root diameter at the commissural level and the total cusp area agrees closely with other published data.[9]

The pathogenesis of the three large groups of aortic regurgitation in the present series can now be evaluated in light of the above anatomical description. Patients with infective endocarditis posed no conceptual problem since there was a hole in the body of the cusp in all our surgical cases. Patients with chronic rheumatic disease had shrunken, retracted, and thickened cusps and reduction in cusp area relative to a normal aortic root area caused regurgitation.

In the patients with non-inflammatory aortic root disease the cusps were structurally normal save for an area of thickening on the free edge thought to be secondary to rather than causative of the aortic regurgitation. The total aortic cusp area is greater than in normal hearts. There was, however, a constant relation between cusp area and aortic root size in normal hearts without aortic regurgitation and as

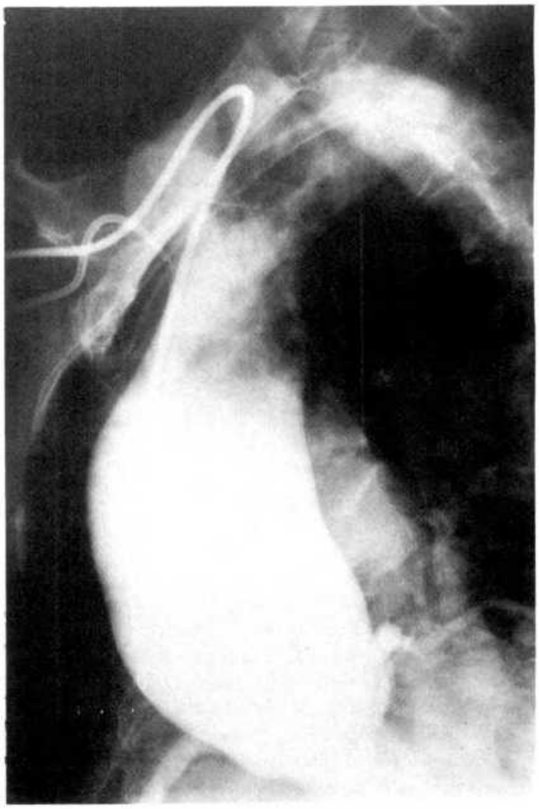

Fig 8 *Aortic regurgitation caused by cusp disease. The normal architecture of the root including the waist marking the insertion of the upper border of the aortic ring into the root of the aorta is effaced.*

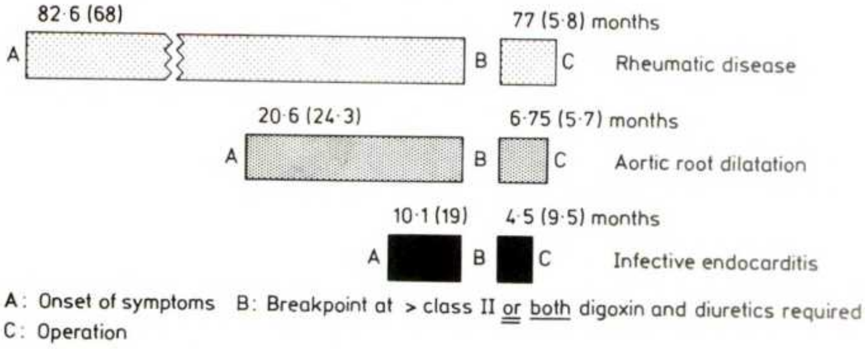

Fig 9 *Onset of symptoms, breakpoint increase in symptoms (> New York Heart Association class II or a requirement for both digitalis and diuretics), timing of surgery in patients with aortic regurgitation caused by rheumatic disease, aortic root dilatation, and infective endocarditis.*

the diameter of the aortic root increases with age there is a concomitant increase in cusp area.[9] This suggests that any increase in aortic root size is matched inevitably by some remodelling of the aortic cusps. Regurgitation develops when there is disproportionate or rapid dilatation of the root relative to the increase in cusp size. Symmetrical dilatation of the upper border of the aortic sleeve causes a central defect that cannot be closed by the cusps. One cusp often has a straight free edge forming a "bow string" across the aortic root (fig 12). If the dilatation is eccentric one cusp may lie at a different level to its abutting neighbour (fig 13).

No differences were noted in the size of the aortic ring at the level of the prosthetic valve suture line in groups of patients with aortic regurgitation of differing aetiologies, and this reinforces the view that the ventricular aspect of the aortic ring is largely irrelevant to the causation of aortic regurgitation.

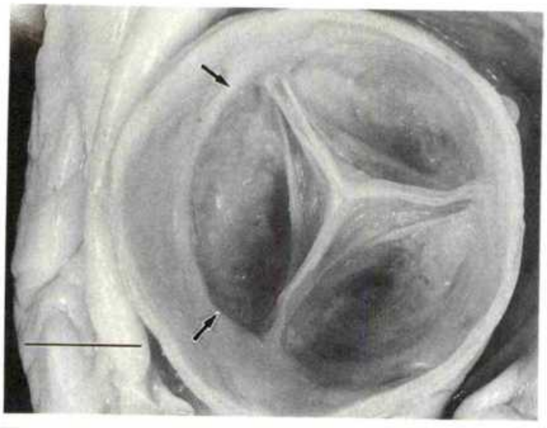

Fig 10 *Normal aortic valve viewed from the aorta after fixation in the closed position by a pressure head of 100 mm Hg formal saline. The valve cusps are tightly apposed. The sinuses bulge outward and there is a distinct ridge (arrows) where the upper aortic valve ring joins the aorta. The commissures of the valve are attached to this ridge. Bar = 1 cm.*

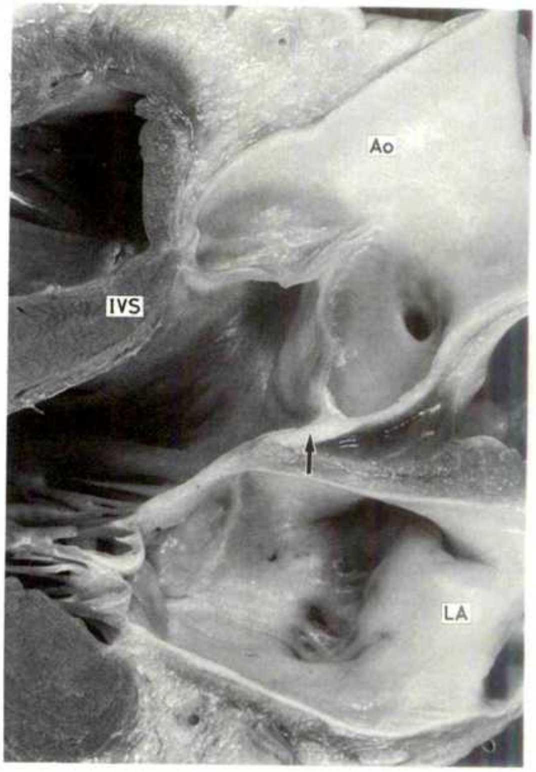

Fig 11 *Long axis transection of the normal aortic root. The lower border of the aortic ring just below the cusps is formed in part by the muscle of the interventricular septum (IVS) and also by the base of the anterior cusp of the mitral valve (arrow). Ao, aorta; LA, left atrium.*

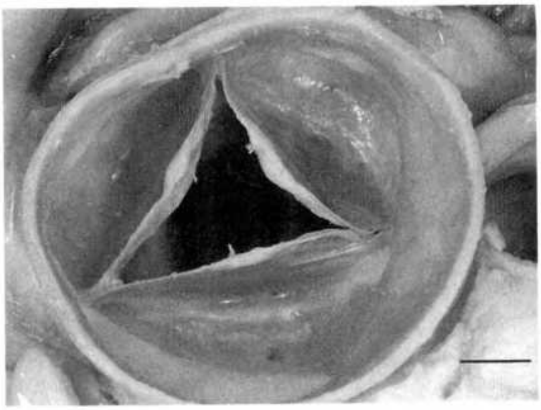

Fig 12 *Aortic valve in a case of aortic regurgitation caused by root dilatation. (Fixation as in fig 10.) The whole aortic root has dilated leaving a large central defect where the cusps fail to appose. The cusps have normal bodies but distinct rolled fibrous edges. Root diameter 4·5 cm. Bar = 1 cm.*

On the contrary, the upper border of the aortic ring or annulus, which provides most of the support for the valve cusps at their commissures, is of vital importance and when its structural integrity is compromised important aortic regurgitation results.

In keeping with this view, Reeves *et al* reported a lack of correlation between echocardiographic measurements of supposed aortic root size and that indicated by the size of the prosthetic valve.[10] This could have been predicted since the echo beam traverses the aorta at the level of the top of the commissures, whereas it is the lower portion of the aortic ring at the base of the cusps, not measured by echocardiography, to which the prosthesis is sutured. It is clearly vital to define the exact site of "aortic root" measurements.

The appearance of symptoms in aortic regurgitation depend in large measure upon the ability of the left ventricle to handle a diastolic volume load. In the short term the amount of regurgitant flow depends on the size of the regurgitant orifice, the duration of diastole, the gradient between aortic diastolic pressure and left ventricular end diastolic pressure, and the distensibility or compliance of the left ventricle. The conventional view appears to be that in the chronic state it is not the amount of regurgitation that changes, but rather the ventricle.[11–13] This may be true in patients with chronic rheumatic valvulitis, in which the progress of scarring and retraction of the cusps change very slowly and this allows time for the left ventricle to compensate. Only when the compensatory mechanisms fail do symptoms occur.

In patients with non-inflammatory root disease it is not difficult to envisage an increase in the size of the regurgitant orifice as the root dilates and the upper aortic ring enlarges; the ventricle is therefore required to compensate not for a constant amount of regurgitation but for one which increases with time.

The present study accords closely with an analysis of the aetiology of 225 cases of pure aortic regurgitation coming to surgery over a 15 year period at the Mayo Clinic[14] which also emphasises that aortic root dilatation is now a common cause of pure aortic regurgitation in Western populations. Several groups have described aortic root dilatation both in Marfan's syndrome and what are regarded as "formes frustes" without any other manifestation of Marfan's syndrome known as annulo-aortic ectasia; in all these reports aortic regurgitation was attributed to aortic root dilatation.[15–17]

In contrast others have described a condition in which regurgitation has been attributed to "floppy" aortic cusps.[18–20] It is postulated that myxoid degeneration of cusp tissue leads to enlargement of the cusp and prolapse toward the ventricle allowing regurgitation despite a normal aortic root. The condition is regarded as analogous to floppy mitral valves with which it has been described to coexist.[21] The present study and the larger series from the Mayo Clinic[14] do not contain any such cases. The condition does exist (fig 14) and when it is present the cusps are soft, nodular, thickened, and with pronounced elongation of the lunular area despite an aortic root of normal size. Over a 10 year period only two cases have been seen at St George's Hospital; neither is reported in the present series.

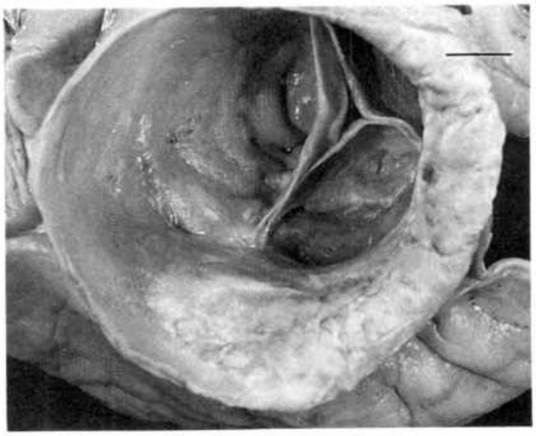

Fig 13 *Aortic valve in a case of aortic regurgitation caused by root dilatation. (Fixation as in fig 10.) The supra-aortic ridge associated with one sinus is lost and the root is dilated. The cusp related to the dilated sinus lies at a higher level than the other cusps. Bar = 1 cm.*

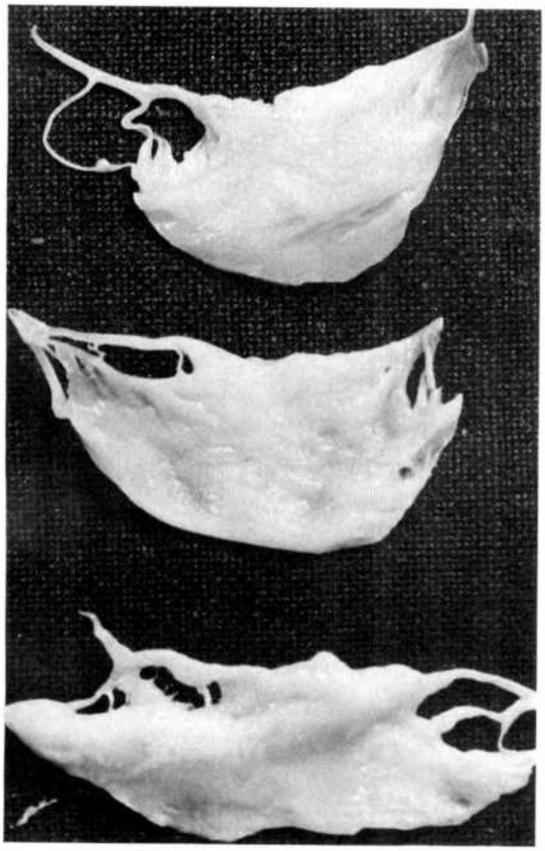

Fig 14 *Valve cusps from a case of aortic regurgitation caused by "floppy" aortic valve cusps. The cusps are nodular and thickened without an appreciable increase in surface area. Unlike the cusps in rheumatic disease these felt soft and pliable; the lunulae of the cusps are elongated. The dimensions of the aortic root were normal.*

Histologically the cusp fibrosa is disrupted and contains an excess of acid connective tissue mucins.

One study of 55 cases of aortic regurgitation ascribed 13 cases to floppy cusps but it may be significant that the size of the aortic root was not measured.[20] A study from Italy found 12 (7·3%) floppy aortic valves in 177 cases of pure aortic regurgitation.[22] There may either be a true geographical variation or different morphological definitions of what is called a "floppy" aortic valve. Before a separate primary abnormality of the cusps is diagnosed the aortic root which supplies structural support for the cusps must be seen to be normal in size and morphology. Patients with mitral valve prolapse without Marfan's syndrome do not usually have aortic root dilatation.[23]

There may be a fundamental difference between patients with isolated aortic regurgitation caused by aortic root dilatation and those with mitral regurgitation caused by floppy valves. The former problem is marked by disruption or dissolution of elastic tissue in the aortic root and the valve leaflets are normal. The primary defect in mitral valve prolapse is one of collagen rather than of elastic fibres.[24 25]

Roberts *et al* have reported bicuspid valves and isolated aortic regurgitation in which the anatomical abnormalities and inequality in cusp size appear such that an additional abnormality of the aortic wall is not required to explain the regurgitation.[26] These patients are similar to six of our patients with bicuspid valves and normal histology of the aortic root. Echocardiographic study has demonstrated prolapse of the larger cusp in bicuspid aortic valves[21] and while minor prolapse is common in patients with bicuspid valves severe prolapse is directly related to regurgitation.[27] The five other patients in our series who had bicuspid valves without other gross abnormality of the cusps had additional non-inflammatory aortic root disease. The number of patients in our series with both aortic root dilatation and bicuspid valves is so small that no firm conclusion should be drawn on whether this is simply a chance association or whether there is a genetic link between bicuspid aortic valves and aortic medial degeneration. The increased risk of dissecting aneurysms in the ascending aorta[28 29] associated with bicuspid valves, however, does support the concept of concomitant aortic medial disease.

The important clinical message from our investigation is that isolated primary dilatation of the upper aortic ring is a common cause of aortic regurgitation and is of particular importance because it is likely to progress much more rapidly than rheumatic aortic regurgitation. With the decline in rheumatic disease in Western populations isolated aortic root dilatation will become relatively more common.

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References

1 Rapaport E. Natural history of aortic and mitral valve disease. *Am J Cardiol* 1975;**35**:221–7.

2 Goldschlager N, Pfeifer J, Cohn K, Popper R, Selzer A. The natural history of aortic regurgitation: a clinical and hemodynamic study. *Am J Med* 1973; **54**:557–88.

3 Rotman M, Morris JJ Jr, Behar VS, Peter RH, Kong

Y. Aortic valvular disease: comparison of types and their medical and surgical management. *Am J Med* 1971;**51**:241–57.

4 Samuels DA, Curfman GD, Friedlich AL, Buckley MJ, Austen WG. Valve replacement for aortic regurgitation: long-term follow-up with factors influencing the results. *Circulation* 1979; **60**:647–54.

5 Romhilt DW, Estes EH. A point score system for the ECG diagnosis of left ventricular hypertrophy. *Am Heart J* 1968;**75**:752–8.

6 Feigenbaum H. *Echocardiography*. 3rd ed. Philadelphia: Lea and Febiger, 1981:60–76.

7 Dixon WJ, Brown MB, Engelman L, *et al*. *BMDP statistical software*. Berkeley: University of California Press, 1981.

8 Dinsmore RE, Miller SW. Angiography in acquired valvular heart disease. *Semin Roentgenol* 1979; **14**:153–66.

9 Silver MA, Roberts WC. Detailed anatomy of the normally functioning aortic valve in hearts of normal and increased weight. *Am J Cardiol* 1985;**55**:454–61.

10 Reeves WC, Ettinger V, Thomson K, *et al*. Limitations in the echocardiographic assessment of aortic root dimensions in the presence of aortic valve disease. *Radiology* 1979;**132**:411–3.

11 Henry WL, Bonow RO, Borer JS, *et al*. Observations on the optimum time for operative intervention for aortic regurgitation. I. Evaluation of the results of aortic valve replacement in symptomatic patients. *Circulation* 1980;**61**:471–83.

12 Henry WL, Bonow RO, Rosing DR, Epstein SE. Observations on the optimum time for operative intervention for aortic regurgitation. II. Serial echocardiographic evaluation of asymptomatic patients. *Circulation* 1980;**61**:484–92.

13 Bonow RO, Borer JS, Rosing DR, *et al*. Preoperative exercise capacity in symptomatic patients with aortic regurgitation as a predictor of postoperative left ventricular function and long-term prognosis. *Circulation* 1980;**62**:1280–90.

14 Olson LT, Subramanian R, Edwards WD. Surgical pathology of pure aortic insufficiency: a study of 225 cases. *Mayo Clin Proc* 1984;**59**:835–41.

15 McKusick VA, Logue RB, Bahnson HT. Association of aortic valvular disease and cystic medial necrosis of the ascending aorta. Report of 4 instances. *Circulation* 1957;**16**:188–94.

16 Weaver WF, Edwards JE, Brandenburg RO. Idiopathic dilatation of the aorta with aortic valvular insufficiency: a possible forme fruste of Marfan's syndrome. *Mayo Clin Proc* 1959;**34**:518–22.

17 Cooley DA. Annuloaortic ectasia. *Ann Thorac Surg* 1979;**28**:303–4.

18 Rippe JM, Angoff G, Sloss LV, Wynne J, Alpert JS. Multiple floppy valves: an echocardiographic syndrome. *Am J Med* 1979;**66**:817–24.

19 McKay R, Yacoub MH. Clinical and pathological findings in patients with "floppy" valves treated surgically. *Circulation* 1973;**48** (suppl III):1163–73.

20 Allen WM, Matloff JM, Fishbein MC. Myxoid degeneration of the aortic valve and isolated aortic regurgitation. *Am J Cardiol* 1985;**55**:439–44.

21 Shapiro LM, Thwaites B, Westgate C, Donaldson R. Prevalence and clinical significance of aortic valve prolapse. *Br Heart J* 1985;**54**:179–83.

22 Bellitti R, Caruso A, Festa M, *et al*. Prolapse of the "floppy" aortic valve as a cause of aortic regurgitation. A clinico-morphological study. *Int J Cardiol* 1985;**9**:399–410.

23 Brown OR, Demots SH, Kloster FE, Roberts A, Menashe JD, Beals RK. Aortic root dilatation and mitral valve prolapse in Marfan's syndrome: an echocardiographic study. *Circulation* 1975;**52**:651–7.

24 King BD, Clark MA, Babs N, Kilman JW, Wooley CF. "Myxomatous" mitral valves: collagen dissolution as the primary defect. *Circulation* 1982;**66**:288–96.

25 Gravanis MB, Campbell WG. The syndrome of prolapse of the mitral valve. *Arch Pathol Lab Med* 1982;**106**:369–74.

26 Roberts WC, Morrow AG, McIntosh CL, Jones M, Epstein SE. Congenitally bicuspid valve causing severe pure aortic regurgitation without superimposed infective endocarditis. *Am J Cardiol* 1981;**47**:206–9.

27 Stewart WJ, King ME, Gillam LD, Guyer DE, Weyman AE. Prevalence of aortic valve prolapse with bicuspid aortic valve and its relation to aortic regurgitation: a cross sectional echocardiographic study. *Am J Cardiol* 1985;**54**:1277–82.

28 Edwards WD, Leaf DS, Edwards JE. Dissecting aortic aneurysm associated with congenital bicuspid aortic valve. *Circulation* 1978;**57**:1022–5.

29 Larson EW, Edwards JE. Risk factors for aortic dissection—a necropsy study of 161 cases. *Am J Cardiol* 1984;**53**:849–55.

Br Heart J 1987;58:369–73

Balloon dilatation of unoperated aortic coarctation: immediate results and one year follow up

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SUMMARY Fifteen patients aged 1–19 years (mean 10·9) with previously unoperated aortic coarctation underwent percutaneous balloon angioplasty between January 1985 and February 1986. Nine (60%) were hypertensive at presentation. Under general anaesthetic the systolic coarctation gradient was 24–50 mm Hg (mean 29) and the coarctation diameter was 4–9 mm (mean 5·5). Meditech balloon catheters 8–18 mm in diameter were inflated 1–4 times at 410–760 kPa. After dilatation the systolic coarctation gradient decreased to 0–20 mm Hg (mean 6) and the coarctation diameter increased to 7–20 mm (mean 12). One patient developed a fusiform aneurysm of the aorta at the coarctation site immediately after the procedure. At reinvestigation 6–16 months (mean 12·5) after dilatation 14 of the 15 patients were normotensive. In 13 patients the residual coarctation gradient was 0–10 mm Hg (mean 3). Two patients had recoarctation with residual gradients of 20 and 24 mm Hg and underwent successful repeat dilatation. One patient had developed a small discrete aneurysm at the coarctation site.

Balloon angioplasty is thus a safe and effective method of relieving unoperated aortic coarctation. The frequency of aortic aneurysm and recoarctation is small and probably related to balloon size. This early experience is encouraging , but long term results and further experience are required before this approach is used to treat coarctation generally.

Surgical treatment has greatly improved the long term prognosis in patients with coarctation of the aorta. However, while operation may repair the aorta, long term follow up studies indicate that it does not cure the patient.[1]

Relief of coarctation by balloon angioplasty is now feasible[2-4] and, in view of the higher operative morbidity and mortality associated with reoperation, has been proposed as the first line treatment of postoperative restenosis of coarctation.[5] Vascular complications and the transient benefit from angioplasty have limited the use of this technique in infancy.[6]

Balloon angioplasty achieves its effect by disrupting the intima and media at the site of the coarctation.[7 8] Concern over the possibility of late aneurysm formation at the site of dilatation[9 10] has also restricted the adoption of the technique for relief of unoperated coarctation after infancy.

This report presents the immediate results of balloon angioplasty in a consecutive group of patients over 12 months of age and the results of reinvestigation one year later.

Patients and methods

PATIENTS

Between January 1985 and February 1986 18 patients over the age of 12 months presented to this hospital with unoperated coarctation of the aorta (table). Two patients with associated ductus arteriosus and another with virtual atresia of the aorta were considered unsuitable for angioplasty and were referred for surgery. The remaining 15 patients underwent balloon angioplasty. Their ages ranged from 1 to 19 years (mean 10·9 years). Three patients had associated abnormalities (one had Beckwith's syndrome, one had moderate mitral regurgitation, and the third had moderate aortic valve stenosis).

All patients underwent repeat cardiac catheterisation at 6–16 months (mean 12·5 months) after the initial procedure.

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Table *Details of patients and procedures*

Patient	*Age (yr)*	*Weight (kg)*	*Initial BP (mm Hg)*	*COA gradient (mm Hg)*	*COA diameter (mm)*	*Balloon size (mm)*	*Balloon COA ratio*	*F/U BP (mm Hg)*	*Comments*
1	10	33	145/105	30	4	18	4 5	95/80	Small aneurysm at 12 months
2	1	8	145/80	24	4	15	3 8	110/70	Immediate fusiform aneurysm
3	8	29	120/60	31	5	12	2 4	120/70	
4	11	38	145/85	50	4	15	3 8	115/80	
5	5	19	105/80	26	6	12	2 0	105/70	
6	10	27	110/60	30	6	12	2 0	110/60	
7	10	30	140/70	30	5	12	2·4	120/80	
8	17	55	170/105	30	4	15	3 8	120/70	
9	14	59	125/80	32	7	15	2 1	130/80	
10	17	72	170/90	30	8	18	2 3	150/60	
11	18	69	170/70	24	9	18	2 0	110/70	
12	19	52	170/90	22	7	15	2 1	120/80	
13	6	26	116/76	26	4	10	2 5	110/60	Required repeat angioplasty
14	2	12	120/60	24	5	10	2 0	110/70	Required repeat angioplasty
15	15	58	170/105	26	4	15	3·8	120/80	

BP, blood pressure, COA, coarctation; balloon:COA, ratio of balloon diameter to coarctation diameter, F/U BP, blood pressure on admission for repeat cardiac catheterisation.

METHODS

Informed consent to balloon angioplasty was obtained before investigation in all patients, and all procedures were performed under general anaesthesia. The balloon dilatation was performed during the initial catheterisation in 12 patients. The other three patients had been catheterised before. Catheters were introduced percutaneously via the femoral artery. Initial assessment included simultaneous measurement of pressure in the ascending aorta and femoral artery, measurement of withdrawal pressure across the site of coarctation, and a cineaortogram in the left anterior oblique projection. The diameter of the aorta above the coarctation was measured from a freeze frame image on a video monitor with correction for magnification from the known diameter of the cardiac catheter. A balloon size that was 1 to 2 mm smaller than the aortic diameter was chosen. The balloon catheters (Meditech) were introduced percutaneously without an arterial sheath and were advanced to the site of the coarctation over a guide wire. Dilute radiographic contrast medium was used for balloon inflation, with accurate positioning of the balloon being assessed by the appearance of a waist at the site of coarctation. The balloon was inflated at pressures between 410–760 kPa. If waisting was not produced the position of the balloon was adjusted and the procedure was repeated. No patient had more than four balloon inflations. The duration of inflation varied but did not exceed 15 seconds.

After deflation the balloon catheter was withdrawn but the guide wire was left in place across the coarctation site. An end-hole catheter was positioned in the aortic arch for repeat simultaneous measurement of pressure in the ascending aorta and femoral artery and angiography. After the procedure haemostasis was achieved by femoral artery compression. Patients were monitored closely in the recovery period, with particular attention being paid to the peripheral pulses and blood pressure, and all had a postoperative chest *x* ray to detect mediastinal widening. Patients rested in bed for 24 hours and were allowed home on the second postoperative day. All were prescribed oral atenolol for one month.

During the course of the study certain modifications were made to the above procedure. Patients 1–3 were not heparinised during the dilatation procedure because of the possible risk of intramural haemorrhage after angioplasty. As this did not prove to be a problem we felt that the risk of embolism related to the prolonged use of guide wires during the procedure was greater and so patients 4–15 were anticoagulated with 100 units/kg of sodium heparin before the introduction of the guide wire. Pressure recordings from the right radial and the contralateral femoral artery are now monitored throughout the procedure so that the residual gradient can be measured without withdrawing the balloon catheter completely, thereby avoiding unnecessary trauma to the femoral artery.

Results were compared by Student's paired *t* test as appropriate.

Results

Nine (60%) of the 15 patients were hypertensive on presentation (table). Under general anaesthesia the pressure gradient across the coarctation ranged from 24 to 50 mm Hg (mean 29 mm Hg) (fig 1). The diameter of the aorta immediately above the coarctation ranged from 6 to 23 mm and at the coarctation from 4 to 9 mm (mean 5·5 mm) (fig 2). These measurements were taken from cineangiograms developed after the procedure. The balloon catheters used for dilatation were between 8 and

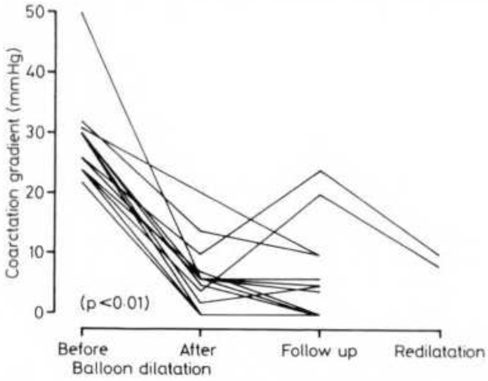

Fig 1 *Systolic pressure gradient across the coarctation before and after balloon dilatation, at the one year follow up catheterisation, and after repeat dilatation (two patients). Two pairs of patients had identical results.*

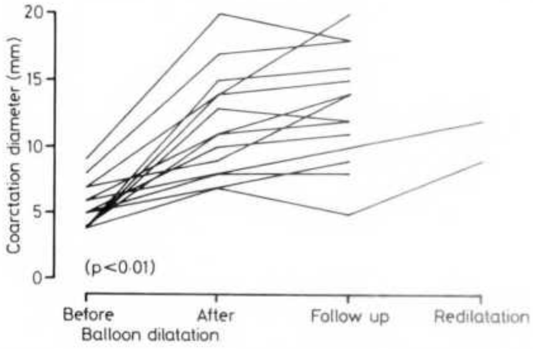

Fig 2 *Diameter of the aorta at the coarctation before and after balloon dilatation, at the one year follow up catheterisation, and after repeat dilatation (two patients). Two patients had identical results.*

18 mm in diameter. The ratio of the balloon diameter to coarctation diameter was between 2 and 2·5 in all but five patients (table).

Immediately after balloon inflation the pressure gradient across the site of coarctation was reduced to 0–20 mm Hg (mean 5·7 mm Hg; $p < 0·01$). On repeat angiography the diameter of the coarctation had increased significantly to 7–20 mm (mean 11·8 mm; $p < 0·01$). In patient 2 a fusiform aneurysm of the coarctation site was produced (fig 3). The ratio of the balloon to coarctation diameter in this patient was 3·8.

After the dilatation few vascular problems were seen. In particular, there were no embolic complications and post-dilatation hypertension did not occur. The right femoral artery pulse was weak in only one patient at one year. The clinical signs of coarctation resolved in all patients and no patient became hypertensive after the atenolol was withdrawn. One patient had systolic hypertension and all others were normotensive at the time of their repeat cardiac catheterisation.

At recatheterisation the residual coarctation gradient was between 0 and 24 mm Hg (mean 5·6 mm Hg). In 11 patients the residual gradient was ≤10 mm Hg and the angiographic appearances were satisfactory with no sign of aortic dilatation or aneurysm (fig 4). Two patients had developed haemodynamic and angiographic evidence of restenosis and underwent successful repeat dilatation. There was a small discrete aneurysm at the coarctation site in patient 1 (fig 5) in whom the balloon to coarctation diameter ratio was 4·5. There had been no change in the angiographic appearance of the fusiform aneurysm in patient 2 (fig 3). No patient has subsequently required operation. Long term follow up of all patients is continuing.

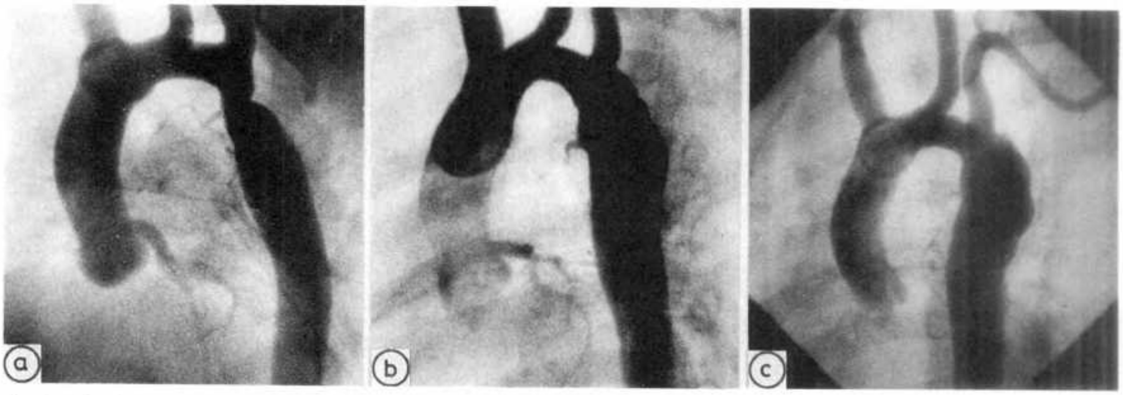

Fig 3 *Aortic angiogram in patient 2 before (a) and after (b) dilatation and at one year follow up (c). Note the fusiform aneurysm of the aorta at the site of coarctation immediately after dilatation (b). There was no significant change over the following year (c). Balloon:coarctation ratio 3·8.*

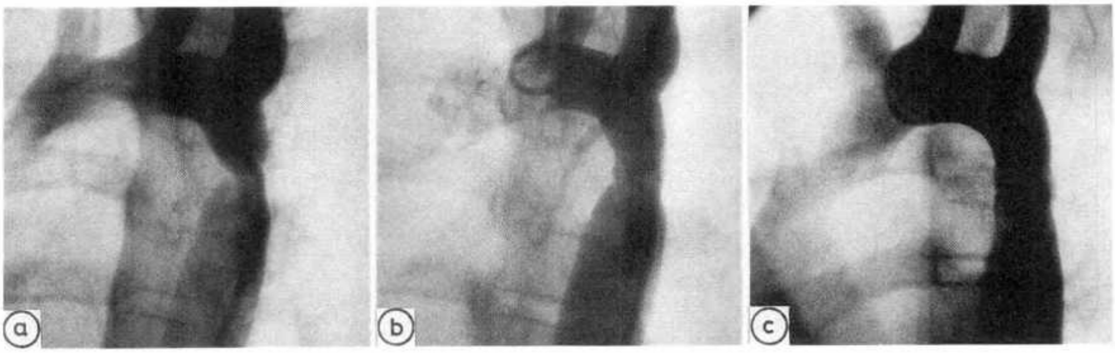

Fig 4 *Arch aortogram in patient 9, demonstrating successful balloon dilatation which has been maintained at one year. Balloon:coarctation ratio 2·4.*

Discussion

Although the immediate results of operative treatment of coarctation of the aorta are good, it carries a small but significant morbidity. Late mortality is usually related to cardiovascular problems, particularly residual hypertension. Restenosis or aneurysm may develop, the latter particularly after patch aortoplasty.[11 12] Even selected normotensive patients with good operative results have abnormalities such as residual left ventricular hypertrophy and hyperkinesia.[1] Hypertension may occur on exercise, even if there is no residual coarctation, and is probably related to abnormal vascular tone in the upper half of the body.

Because balloon angioplasty achieves its effect by disruption of the intima and media of the aortic wall, there is concern over the possibility of aneurysm formation.[9 10 13] Balloon angioplasty has been proposed as the treatment of choice for restenosis of coarctation because the risk of late aneurysm formation is probably less than the problems associated with repeat operation.[5] If long term follow up shows a low incidence of aneurysm and other problems, balloon angioplasty may also be preferred to surgical resection of unoperated coarctation.

There are few reports of the development of aneurysms after balloon dilatation of native coarctation.[3 10] Cooper *et al* found aneurysms in three (43%) of seven children after the use of balloons 1 mm smaller than the diameter of the aorta proximal to the coarctation.[3] They did not compare balloon diameter with coarctation diameter. Marvin *et al* reported that six (55%) of eleven children developed aortic aneurysms after 7–14 months.[10] In these patients the balloons used for dilatation were 2·5–3 times larger than the diameter of the coarctation determined angiographically. All six aneurysms were

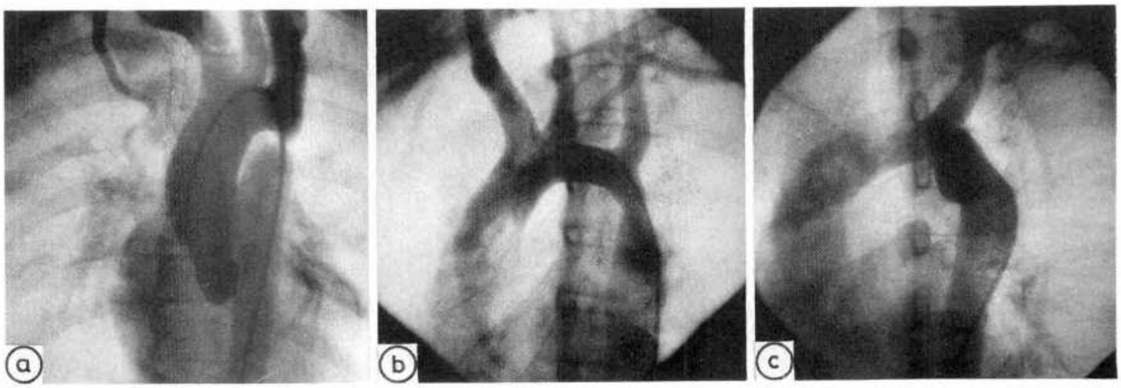

Fig 5 *Aortic angiogram in patient 1 before (a) and after (b) balloon dilatation. Repeat angiogram at one year (c) shows a small saccular aneurysm at the coarctation site. Balloon:coarctation ratio 4·5. Frame (a) is the anteroposterior projection while (b) and (c) are left anterior oblique views.*

resected at operation because of the angiographic appearances. Our results do not confirm this high incidence of early aneurysm development, and neither fusiform nor saccular aneurysm formation was seen in any patient with a balloon to coarctation ratio <3·8.

Various technical aspects of the procedure may influence its efficacy and also the risk of late complications. They will be assessed only by longer follow up of greater numbers of patients. Larger balloons may produce better relief of coarctation at the expense of a higher incidence of late aneurysm. The only aneurysm we found at follow up angiography (fig 5) occurred in the patient with the highest balloon to coarctation ratio. The rate of balloon inflation, the number of inflations, the maximum pressure achieved, and the duration of inflation may also affect immediate and long term results but no data are available to confirm this. Since measurement of the aortic diameter from the video monitor is inaccurate, we now correct for magnification by using a calibrated marker catheter. It may be that the diameter of the coarctation is a better guide to the selection of balloon size than the aortic diameter but the coarctation is difficult to measure accurately. Although the balloon size necessary for relief of pulmonary valve stenosis can, in our experience, be predicted from the body weight or body surface area, no such relation exists in patients with coarctation.

Balloon dilatation of aortic coarctation is effective in relieving the obstruction and associated systemic hypertension. Our results suggest that the frequency of aneurysm development at early reassessment is much less than has been reported previously and that aneurysm development may be avoidable. These early results are encouraging but long term follow up will be necessary before balloon angioplasty can be confirmed as a safe and effective alternative to surgical resection for the primary relief of aortic coarctation.

References

1 Carpenter MA, Dammann JF, Watson DD, Jedeikin R, Tompkins DG, Better GA. Left ventricular hyperkinesia at rest and during exercise in normotensive patients 2 to 27 years after coarctation repair. *J Am Coll Cardiol* 1985;**6**:879–88.

2 Lababidi ZA, Daskalopoulos DA, Stoeckle H Jr. Transluminal balloon angioplasty: experience with 27 patients. *Am J Cardiol* 1984;**54**:1288–91.

3 Cooper RS, Ritter SB, Rothe WB, Chen CK, Griepp R, Golinko RJ. Angioplasty for coarctation of the aorta: long-term results. *Circulation* 1987;75:600–4.

4 Lock JE, Bass JL, Amplatz K, Fuhrman BP, Castaneda-Zuniga W. Balloon dilation angioplasty of aortic coarctation in infants and children. *Circulation* 1983;**68**:109–16.

5 Lock JE, Keane JF, Fellows KE. The use of catheter intervention procedures for congenital heart disease. *J Am Coll Cardiol* 1986;7:1420–3.

6 Finley JP, Beaulieu RG, Nanton MA, Roy DL. Balloon catheter dilatation of coarctation of the aorta in young infants. *Br Heart J* 1983;**50**:411–5.

7 Lock JE, Niemi T, Burke BA, Einzig S, Castaneda-Zuniga WR. Transcutaneous angioplasty of experimental coarctation. *Circulation* 1982;**66**:1280–6.

8 Lock JE, Castaneda-Zuniga WR, Bass JL, Foker JE, Amplatz K, Anderson RW. Balloon dilatation of excised aortic coarctations. *Radiology* 1982;**143**:689–91.

9 Bull C. Interventional catheterisation in infants and children. *Br Heart J* 1986;**56**:197–200.

10 Marvin WJ, Mahoney LT, Rose EF. Pathological sequelae of balloon dilatation angioplasty for unoperated coarctation of the aorta in children [Abstract]. *J Am Coll Cardiol* 1986;7:117A.

11 Ala-Kulju K, Jarvinen A, Maamies T, Mattila S, Merikallio E. Late aneurysms after patch aortoplasty for coarctation of the aorta in adults. *Thorac Cardiovasc Surg* 1983;**31**:301–5.

12 Hehrlein FW, Mulch J, Rautenburg HW, Schlepper M, Scheld HH. Incidence and pathogenesis of late aneurysms after patch graft aortoplasty for coarctation. *J Thorac Cardiovasc Surg* 1986;**92**:226–30.

13 Lock JE. Now that we can dilate, should we? *Am J Cardiol* 1984;**54**:1360.

Br Heart J 1987;58:374–7

Operative balloon dilatation for pulmonary atresia with intact ventricular septum

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SUMMARY In six infants with pulmonary atresia and intact ventricular septum operative balloon dilatation was used to achieve continuity between the right ventricle and the main pulmonary artery as the initial procedure. Two of the six subsequently needed an aortico pulmonary shunt. All six are alive and well.

Pulmonary atresia with intact ventricular septum is a rare abnormality, which is usually lethal within the first few weeks of life.[1] Surgical results have improved after the introduction of prostaglandin E infusion to maintain ductal patency[2] thus permitting the surgeon to operate on infants who are in better biochemical and haemodynamic condition. It is generally agreed that operation should provide not only adequate pulmonary blood flow but also anterograde flow through the right ventricular outflow tract in order to decompress the ventricle and encourage growth of both the right ventricle and the tricuspid valve ring. Recent papers have recommended valvotomy combined with a shunt procedure, either via a right thoractomy with a Waterston shunt[3] or a left sided approach combining a modified Blalock-Taussig shunt with transpulmonary valvotomy.[4]

Percutaneous balloon valvuloplasty for pulmonary stenosis[5-7] has given encouraging initial results. We therefore decided to attempt dilatation of the atretic pulmonary valve using a balloon introduced via the right ventricle at operation. This paper presents our initial experience.

Patients and methods

Over a ten month period in 1986, six consecutive infants presenting with pulmonary atresia and intact ventricular septum were managed with an initial operative pulmonary balloon dilatation. According to the classification of Bull and colleagues,[8] all our cases had a hypoplastic but tripartite right ventricle (inlet, trabecular, and infundibular portions) with patency of the right ventricular outflow tract up to the level of the imperforate valve. The tricuspid valve annulus measured on the preoperative angiogram (4 cases) or echocardiogram (2 cases) varied in diameter from 7 to 12 mm. The figure shows a typical angiogram. They are therefore in the group which would seem to have an anatomy which is most favourable from the surgical viewpoint. The table gives details of the patients.

All infants were treated initially with intravenous prostaglandin E infusion after echocardiographic diagnosis. Operative balloon dilatation was performed after angiography and balloon atrial septostomy in cases 1, 2, 3, and 4 but patients 5 and 6 were accepted for operation on the basis of the ultrasound examination alone without septostomy. Patient 3 was stabilised on oral prostaglandin[9] but was then readmitted with increasing cyanosis at nine weeks of age.

A median sternotomy was used in all cases and the heart was elevated by swabs placed in the posterior pericardium. A standard 10 mm external diameter balloon dilatation catheter was used (Meditech). The balloon catheter was tested to assess the volume of saline required to produce a firm inflation. A purse-string suture was placed in the anterior wall of the right ventricle and the catheter was introduced via a stab incision. It was advanced by palpation up to and then through the atretic valve using firm pressure. With the catheter and balloon positioned across the valve ring the balloon was inflated three times with the predetermined volume of saline. Any bradycardia was allowed to recover before reinflation. The catheter was withdrawn and the purse-string tied.

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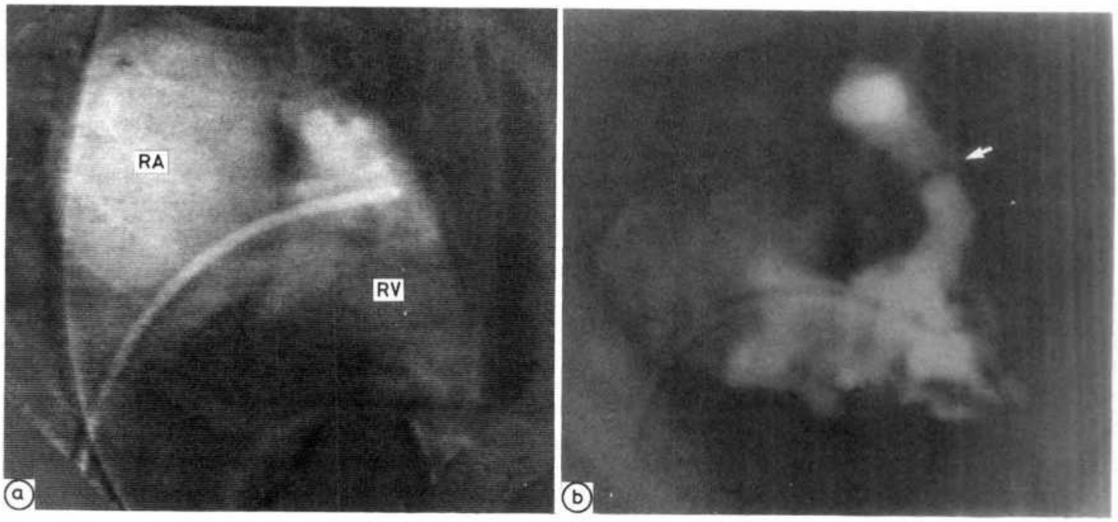

Fig *Right ventricular angiograms in cases 1 and 5. (a) Digital subtraction right ventricular angiogram in patient 1 before operation. The ventricle is well developed up to the level of the imperforate valve but the trabecular zone is poorly opacified. There is considerable tricuspid regurgitation. (b) Digital subtraction right ventricular angiogram in patient 5 six months after operation. The right ventricle is tripartite but the trabecular portion is partially obliterated by hypertrophied muscle bundles. The dysplastic, but now perforate, pulmonary valve membrane is arrowed. RA, right atrium; RV, right ventricle.*

Table *Patient details at the time of operation*

Case	*Age (days)*	*Weight (kg)*	*Sex*	*Balloon atrial septostomy*
1	12	3·6	M	+
2	3	2·2	M	+
3	60	3·8	M	+
4	1	3·3	F	+
5	17	3·0	M	–
6	2	3·6	M	–

Results

The valve was felt to "give" in each case during inflation. The length of the standard dilatation catheter caused problems, however. In one infant (case 4) inflation produced a tear in the right ventricular outflow tract, resulting in considerable blood loss. In case 2 this problem was anticipated because the baby was so small and the technique was modified. An embolectomy catheter was used instead, and the inflated balloon was withdrawn across the valve.

Prostaglandin E infusion was continued in all the infants postoperatively until blood gases were satisfactory. Prostaglandin treatment could not be withdrawn in cases 4 and 5 and Waterston shunts were constructed 14 and 21 days after the dilatation. The remaining patients were extubated 1, 3, 5, and 7 days after operation. All six patients are alive, gaining weight, and developing normally 6–16 months after operation (median 11 months). Patient 5 underwent an uneventful repair of a cleft palate four months after the dilatation. Re-evaluation by cardiac catheterisation was carried out at six months and showed that right ventricular pressure was 75% of the systemic pressure. He is now awaiting surgical reconstruction of the right ventricular outflow tract. Postoperative Doppler ultrasound examination of cases 1, 2, 3, 4, and 6 showed a pressure drop of 15, 80, 40, 10, and 20 mm Hg respectively between the right ventricle and the main pulmonary artery. Patient 2 was recatheterised six months after the procedure. The investigation confirmed a high right ventricular pressure but the pulmonary valve could not be crossed. However, the right ventricular cavity was well developed and no tricuspid regurgitation was detected. He recently underwent successful reconstruction of his right ventricular outflow tract on cardiopulmonary bypass.

Discussion

Before the introduction of prostaglandin infusion to maintain ductal patency the results of pulmonary valvotomy alone as the initial palliative measure for these infants were very poor with some workers reporting 100% mortality.[3] As a result systemic to pulmonary artery shunts were advocated but follow up of these patients demonstrated lack of development of the right ventricle and tricuspid valve. A morphological study by Bull and colleagues showed that the small right ventricular cavity was in many cases caused by massive hypertrophy.[8] It was suggested that this would regress if the ventricle was decompressed. They also suggested that the pulmonary valve annulus was usually adequate to support the circulation and that the limitation to forward flow was the size of the tricuspid valve annulus. In a study from the same group, de Leval *et al* reported angiographic evidence of growth of the tricuspid annulus which was greatest if right ventricle to pulmonary artery continuity was established early in life.[4] On the basis of this, and combined with their poor results with valvotomy alone, they recommend a left thoracotomy and creation of a modified Blalock-Taussig shunt with a transpulmonary valvotomy.

In contrast, Dobell and Grignon argued in favour of an initial valvotomy, performed via a median sternotomy and with Hegar dilators to open the valve.[10] They emphasised that improvement is not immediate and time must be given to allow the oedema to settle. As the right ventricle decompresses the compliance will improve and forward flow will increase.

Whatever the preferred technique, all are agreed that pulmonary artery to right ventricular continuity should be established as soon as possible. It seems unnecessary to use cardiopulmonary bypass to perform an open valvotomy or valvectomy although inflow occlusion during this procedure has been advocated.[11] Blind transventricular valvotomy with dilators cannot offer maximum dilatation and even the advocates of transpulmonary valvotomy in the beating heart (using an embolectomy balloon to occlude the right ventricular outflow) admit that exposure of the pulmonary valve is not ideal.[11] On the basis of our initial experience we feel that the balloon catheter introduced via a small stab incision in the right ventricle circumvents some of these difficulties and offers a rapid, simple method of providing maximum dilatation of the valve with minimal trauma to the ventricle.

In pulmonary atresia with an intact ventricular septum there is a range of right ventricular cavity sizes varying from severely hypoplastic to dilated.[12] Morphological studies[12 13] and surgical series[3 4 10] suggest that cases with a right ventricle which is sufficiently well developed to allow continuity to be established between the right ventricle and the pulmonary artery in the neonatal period without the addition of a pulmonary to systemic artery shunt are in the minority. Nevertheless, these cases should be identifiable at the preoperative imaging study, whether angiography or ultrasound, and they seem to be suitable for a comparatively simple procedure to decompress the right ventricle and establish an adequate pulmonary blood flow. Balloon atrial septostomy was performed in four of our patients because we had previously followed the management plan for these patients outlined by Patel and colleagues.[14] However, if dilatation is to be performed without a shunt then a high right atrial pressure might be desirable in order to promote forward flow of blood through a relatively non-compliant right ventricle. In these circumstances atrial septostomy seems to be contraindicated.

Ring *et al* studied the effects of balloon dilatation on the pulmonary valve annulus in lambs and observed that the main area of trauma was not the annulus but rather the right ventricular outflow tract.[15] We believe this area of trauma results in oedema which can be a major cause of obstruction to blood flow immediately after operation. Accordingly we continued the prostaglandin infusion postoperatively until flow through the valve improved. With this policy, we accept a slower postoperative recovery than if a shunt had been constructed simultaneously, and also accept that a shunt may be necessary in some patients at a later stage if they remain prostaglandin dependent. The considerable advantage is that unnecessary shunts are avoided.

The main problems were associated with the size of the standard dilatation balloon catheter which has a 1 cm tip distal to a 3 cm balloon. In neonatal hearts the tip of this catheter impinges on the bifurcation of the pulmonary artery while the proximal shoulder of the balloon distends the right ventricular outflow tract. A 0·5 cm guiding tip and a 1·5 cm balloon would be more appropriate for use in neonatal hearts and we hope soon to try a modified balloon catheter.

References

1 Freedom RM, Keith JD. Pulmonary atresia with normal aortic root. In: Keith JD, Rowe RD, Vlad P, eds. *Heart disease in infancy and childhood.* 3rd ed. London, New York: Macmillan, 1978:506–17.

2 Olley PM, Cocceani F, Bodach E. E-type prostaglandins. A new emergency therapy for certain cyanotic congenital heart malformations. *Circulation* 1976;**53**:728–31.

3 Moulton AL, Bowman FO, Edie RN, *et al*. Pulmonary atresia with intact ventricular septum: sixteen year experience. *J Thorac Cardiovasc Surg* 1979; **78**:527–36.

4 de Leval M, Bull C, Stark J, Anderson RH, Taylor JFN, Macartney FJ. Pulmonary atresia and intact ventricular septum: surgical management based on a revised classification. *Circulation* 1982;**66**:272–80.

5 Lababidi Z, Jiunn-ren W. Percutaneous balloon pulmonary valvuloplasty. *Am J Cardiol* 1983;**52**:560–2.

6 Kan JS, White RI, Mitchell SE, Anderson JH, Gardner TJ. Percutaneous transluminal balloon

valvuloplasty for pulmonary valve stenosis. *Circulation* 1984;**69**:554–60.

7 Tynan M, Baker EJ, Rohmer J, *et al*. Percutaneous balloon pulmonary valvuloplasty. *Br Heart J* 1985;**53**:520–4.

8 Bull C, de Leval MR, Mercanti C, Macartney FJ, Anderson RH. Pulmonary atresia and intact ventricular septum: a revised classification. *Circulation* 1982;**66**:266–71.

9 Silove ED, Coe JY, Shiu MF, *et al*. Oral prostaglandin E2 in ductus dependent pulmonary circulation. *Circulation* 1981;**63**:682–8.

10 Dobell ARC, Grignon A. Early and late results in pulmonary atresia. *Ann Thorac Surg* 1977;**24**:264–74.

11 Moulton AL, Malm JR. Right ventricular outflow tract obstruction. In: Stark J, de Leval M, eds. *Surgery for congenital heart defects*. London, New York: Grune and Stratton, 1983:305–6.

12 Zuberbuhler JR, Anderson RH. Morphological variations in pulmonary atresia with intact ventricular septum. *Br Heart J* 1979;**41**:281–8.

13 Freedom RM, Dische MR, Rowe RD. The tricuspid valve in pulmonary atresia and intact ventricular septum. *Arch Pathol Lab Med* 1978;**102**:28–31.

14 Patel RG, Freedom RM, Moes CAF, *et al*. Right ventricular volume determinations in 18 patients with pulmonary atresia and intact ventricular septum. Analysis of factors influencing right ventricular growth. *Circulation* 1980;**61**:428–40.

15 Ring JC, Kulik TJ, Burke BA, Lock JE. Morphologic changes induced by dilation of the pulmonary valve annulus with overlarge balloons in newborn lambs. *Am J Cardiol* 1984;55:210–4.

Br Heart J 1987;**58**:378–84

Anomalous left coronary artery from the pulmonary artery: a 15 year sample*

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SUMMARY Eleven patient with anomalous left coronary artery arising from the pulmonary artery were identified from the beginning of 1970 to the end of 1985. The only male patient presented at the age of eight years for assessment of a murmur and was symptom free. The remainder presented in infancy with features of cardiac failure. The electrocardiogram was abnormal in all patients, the majority showing anterolateral ischaemia. Cross sectional echocardiography when available showed a dilated, poorly contracting left ventricle, and in two cases what appeared to be a "normal" origin of the left coronary artery. Aortography was performed in 10 patients and led to the correct diagnosis in eight. The diagnosis was made at necropsy in three infants. One patient has remained well without treatment. The anomalous left coronary artery was ligated in three of the earlier patients, including the asymptomatic boy. Two of these cases had concurrent saphenous vein graft to the anomalous left coronary artery. The four most recent cases were treated by successful direct reimplantation of the anomalous left coronary artery to the aorta when they first presented in infancy. They continue to improve symptomatically and show objective improvement of myocardial function.

In this recent experience supports our policy of early surgical re-establishment of a two coronary system from the aorta.

Anomalous left coronary artery arising from the pulmonary artery is a rare congenital abnormality occurring in approximately 1 in 300 000 live births.[1] It is important to recognise this rare disorder because newer surgical techniques, which permit direct anastomosis of the anomalous left coronary artery to the aorta, have considerably improved both morbidity and mortality.[2] Without treatment the majority of patients develop congestive heart failure once the pulmonary vascular resistance begins to fall and run-off occurs from the right coronary artery to the left coronary artery and then into the pulmonary artery. A coronary "steal" develops, leading to ischaemia and possible infarction and fibrosis of the anterolateral wall of the left ventricle. Such patients die in infancy.[3] An occasional patient whose collateral circulation is developed and effectively distributed may remain symptom free and present late in childhood or adult life.[4 5]

In this report we describe our experience of this rare congenital abnormality and highlight the diagnostic features and changes in management, particularly the move towards early surgical re-establishment of a two coronary artery system.

Patients and methods

A retrospective study was undertaken of all patients in whom anomalous left coronary artery was diagnosed at the Royal Children's Hospital, Melbourne from 1970 to 1985. We reviewed the details of the clinical data, investigations, treatment, and necropsy findings, where available, and noted the outcome of the survivors.

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Results

Eleven patients were diagnosed as having anomalous left coronary artery from 1970 to 1985. Ten were females, nine of whom presented between the ages of 2–5 months with a history of poor feeding, recent weight loss, breathlessness, and often respiratory infection. All had signs of cardiac failure. Development of an apical systolic murmur suggestive of mitral incompetence was common. One child presented at the age of four years for evaluation of mitral incompetence after attending another hospital at three months with an acute illness diagnosed as "bronchiolitis". The only boy in the series was seen at the age of eight years for assessment of a murmur.

All except the symptom free boy had *x* ray evidence of cardiomegaly, often with features of pulmonary congestion and pulmonary collapse or consolidation. In 10 patients the electrocardiogram showed anterolateral ischaemia or actual infarction (fig 1). One patient had evidence of left ventricular hypertrophy. Two patients showed evidence of left atrial hypertrophy and one patient had low voltage complexes.

Cross sectional echocardiography was performed on the last five patients. All had evidence of a poorly contracting dilated left ventricle (fig 2). The anomalous left coronary artery was definitely seen to arise from the main pulmonary artery in only one patient (fig 3). In two others the diagnosis was suspected, while in a further two cases an apparently "normal" left coronary artery was seen to arise from the aortic sinus (fig 4).

Enzyme studies were done on one patient only. Activities were increased at and soon after presentation. A thallium radioisotope scan carried out in one patient showed a somewhat dyskinetic anterolateral segment of the left ventricle.

No further study was undertaken in one patient in whom the echocardiogram was thought to be normal. Cardiac catheterisation was carried out in the remaining 10 patients. In the one patient where the echocardiogram was thought to be diagnostic, aortography confirmed the diagnosis of an anomalous left coronary artery arising from the main pulmonary artery. This vessel filled retrogradely from the dilated right coronary artery and was seen to drain into the main pulmonary artery (fig 5a and b).

In the other nine patients left ventricular angiography showed a dilated, poorly contracting left ventricle with varying degrees of mitral incompetence. One patient also had a small ventricular septal defect and a ductus arteriosus. In this patient a poor quality aortogram did not define the anomalous left coronary

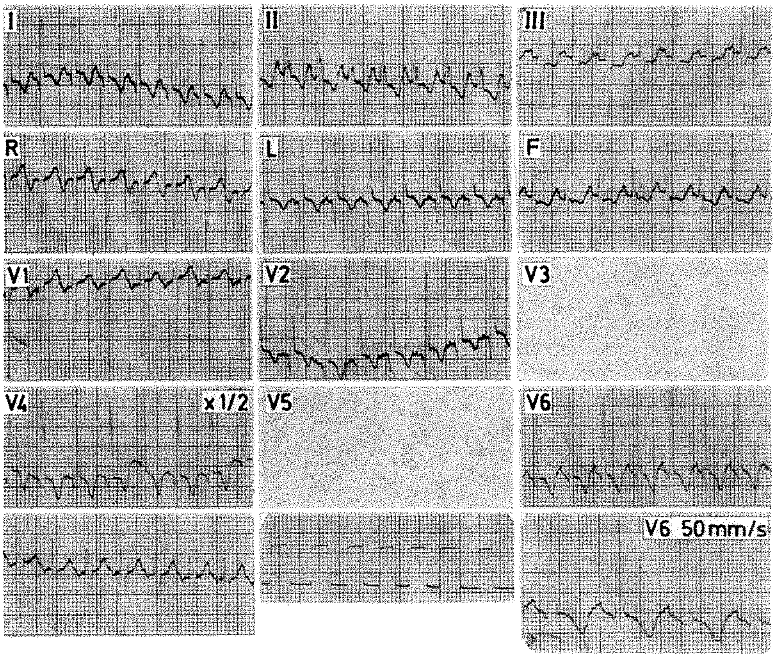

Fig 1 *Electrocardiogram of infant at 10 weeks with anomalous left coronary artery. It shows a Q wave and T wave inversion in I, aVL, and lateral chest leads. There is ST elevation in V2.*

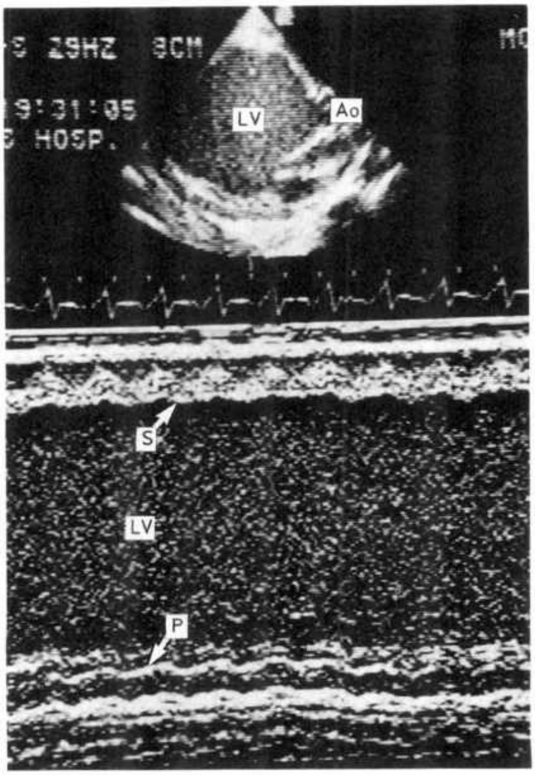

Fig 2 *Cross sectional and M mode echocardiogram of infant at 4 months with anomalous left coronary artery showing grossly dilated, poorly contracting left ventricle. Ao, aorta; LV, left ventricle; S, ventricular septum; P, left ventricular posterior wall.*

artery. In a further infant the aortogram was also of poor quality. The right coronary artery appeared to arise normally and the left coronary artery was filled without its ostium being clearly defined. In the remaining seven patients aortography confirmed the diagnosis of anomalous left coronary artery.

All infants required intensive treatment for cardiac failure. A dopamine infusion was given to two of the more recent patients just before surgery. Two infants died from cardiac failure and respiratory infection at the ages of 9 and 10 months despite intensive medical treatment without antemortem diagnosis of anomalous left coronary artery. A further infant died shortly after ligation of a ductus arteriosus, the diagnosis of anomalous left coronary artery being made at necropsy. One patient has been treated conservatively. She has remained well with stable, moderate mitral incompetence.

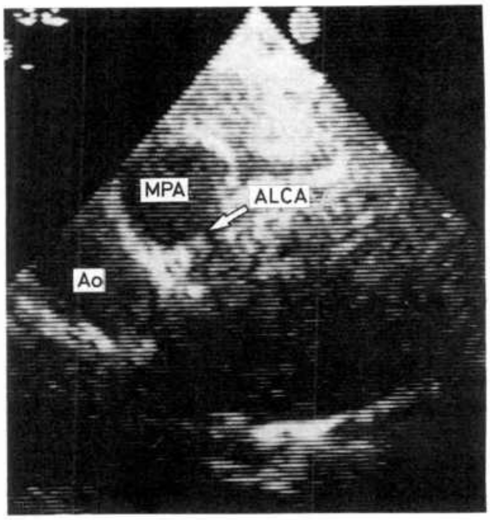

Fig 3 *Cross sectional echocardiogram in high parasternal short axis view showing the anomalous left coronary artery (ALCA) arising from the main pulmonary artery trunk. Ao, aorta, MPA, main pulmonary artery.*

All the other patients were treated by operation. One had ligation of the anomalous left coronary artery at the age of 15 months. She developed effort angina at the age of 12 years and has since had a saphenous vein graft to the left coronary artery. Two other children had ligation of the anomalous left coronary artery as it entered the main pulmonary artery and a concurrent saphenous vein graft to the left coronary artery at the ages of 5 and 8 years. When restudied one and five years later, aortography showed occlusion of the grafts (fig 6). One has since had a mitral valve replacement at the age of 18 years for worsening mitral incompetence.

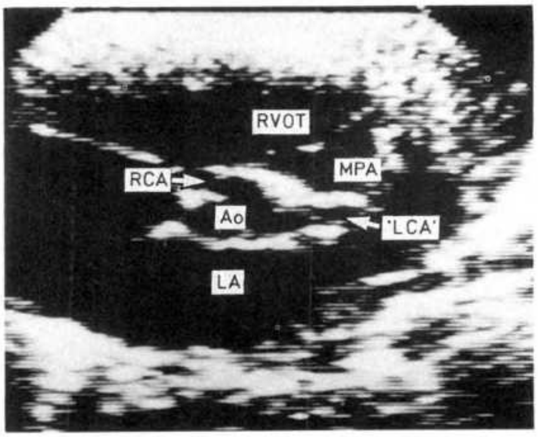

Fig 4 *Cross sectional echocardiogram in parasternal short axis view showing what appears to be a normal left coronary artery arising from the left aortic sinus. Ao, aorta; LA, left atrium; 'LCA', 'left coronary artery'; MPA, main pulmonary artery; RCA, right coronary artery; RVOT, right ventricular outflow tract.*

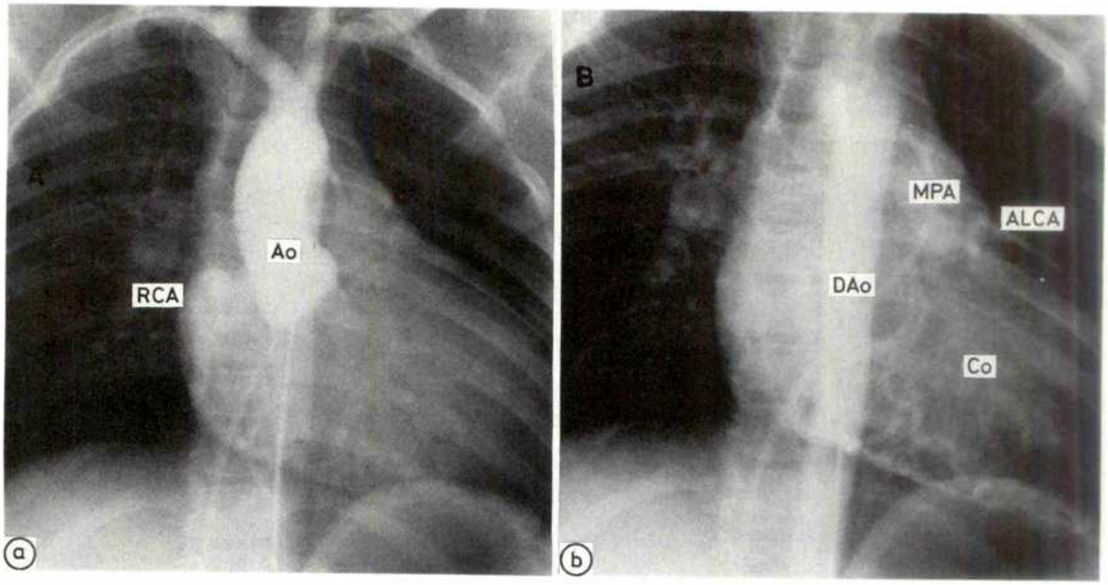

Fig 5 *Aortograms in a patient with an anomalous left coronary artery. (a) Aortic root injection showing filling of a dilated right coronary artery with no filling of the left coronary artery. (b) A later frame showing filling of the left coronary artery via a number of collaterals with subsequent opacification of the main pulmonary artery. Ao, aorta; MPA, main pulmonary artery; RCA, right coronary artery; Co, collaterals.*

In the four most recent patients seen between 1979 and 1985 a direct anastomosis of the anomalous left coronary artery to the aorta was carried out once the diagnosis of anomalous left coronary artery was made. The technique used was that described by Takeuchi *et al*,[2] in which a flap of pulmonary arterial wall is raised to form a coronary tunnel inside the pulmonary artery between a created aortopulmonary window and the left coronary artery ostium. When these patients were restudied six months and one and three years later there was improved contraction of the left ventricle but residual mitral incompetence. The newly anastomosed left coronary artery was patent (fig 7). One patient has developed mild main pulmonary artery stenosis. All four patients have shown considerable improvement in their symptoms, *x* ray, and electrocardiogram and a return towards normal left ventricular function on echocardiography and radionuclide studies. Follow up has lasted from six months to six years. Figure 8 summarises the findings.

Discussion

This review of an Australian sample correlates well with experience in North America and South Africa.[5-7] There was a preponderance of girls and most presented in early infancy with features of cardiac failure. If the anomalous left coronary artery was not recognised early death ensued, with evidence of fibrosis or infarction of the left ventricle at necropsy. However, two patients presented late and one has remained well without operation, as was seen in

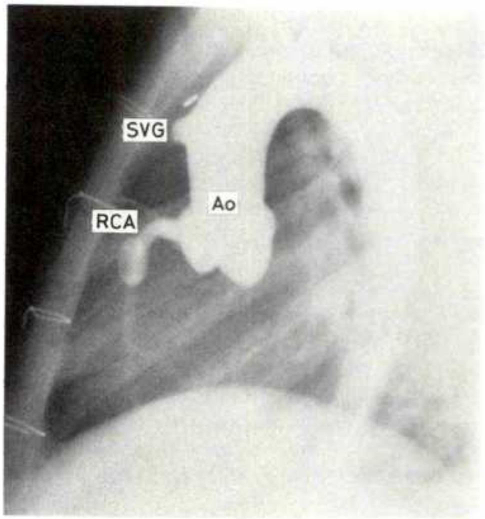

Fig 6 *Aortogram after aortic root injection showing a dilated right coronary artery filling from the right coronary sinus. The occluded stump of the saphenous vein graft is shown. Ao, aorta; RCA, right coronary artery; SVG, saphenous vein graft stump.*

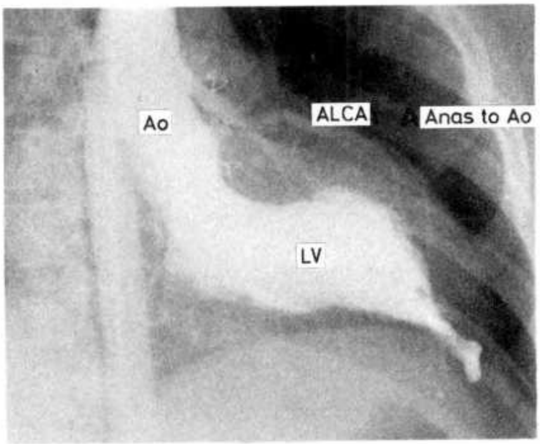

Fig 7 *Left ventricular angiogram three years after a Takeuchi reimplantation of the anomalous left coronary artery to the ascending aorta via a tunnel in the floor of the main pulmonary artery. The left ventricle was contracting well. The angiogram shows the anastomosis to the left coronary artery. Ao, aorta, Anas, anastomosis; LV, left ventricle.*

earlier reports.[4-8] Presumably an effective and well distributed collateral circulation allowed this patient to survive. Long term follow up of such patients suggested that arrhythmias may cause sudden death.[4]

THE DIAGNOSIS OF ANOMALOUS LEFT CORONARY ARTERY

It is difficult to distinguish those patients who present early in cardiac failure with anomalous left coronary artery from those who have congestive cardiomyopathy, usually of uncertain aetiology. Clinical features and radiological assessment are not particularly helpful in identifying the two groups,[6] but if the electrocardiogram shows ischaemic changes it becomes mandatory to seek out an anomalous left coronary artery.[5-6] There are, however, other causes of ischaemic changes in infancy,[5] and the occasional patient with anomalous left coronary artery (one patient in our series) may show left ventricular hypertrophy.[6]

In an extensive study Gutgesell *et al* found that myocardial perfusion imaging with thallium-201 was helpful, but again not diagnostic in distinguishing anomalous left coronary artery from congestive cardiomyopathy.[9]

Several recent studies have extolled the virtues of cross sectional echocardiography.[10-13] All have documented the dilated, poorly contracting left ventricle, doing away with the need for left ventricular angiography. Although some patients were shown to have anomalous left coronary artery arising from the main pulmonary artery trunk, Robinson *et al* emphasised the potential for false negative diagnosis,[13] as we found in two of our cases. The anomalous left coronary artery is in almost an identical position as a normal left coronary artery except that it arises from the pulmonary artery trunk. Robinson *et al* suggested that the echo-free linear structure apparently arising from the aorta and resembling a normal left coronary artery was probably the transverse sinus of the pericardium.[13] Imaging of a dilated right coronary artery was not diagnostic. Our experience with pulsed Doppler is limited. King *et al* suggested that late systolic retrograde flow in the proximal pulmonary artery represented retrograde flow from the anomalous left coronary artery.[12]

Aortography remains essential for definitive diagnosis, but despite such investigation the abnormality

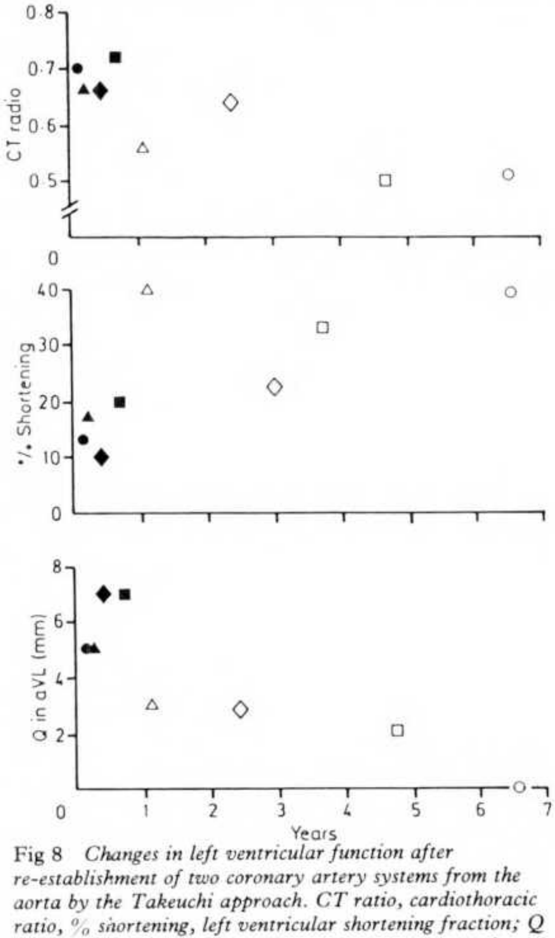

Fig 8 *Changes in left ventricular function after re-establishment of two coronary artery systems from the aorta by the Takeuchi approach. CT ratio, cardiothoracic ratio, % shortening, left ventricular shortening fraction; Q in aVL, depth of Q wave in lead aVL.* ◇, *patient who moved to another state. Black symbols show values before operation. Open symbols are values after operation.*

was missed in two of our cases. In retrospect this result arose from poor quality angiography with lack of clear delineation of the origin of both coronary arteries. Selective right coronary angiography has been especially helpful in demonstrating the dilated right coronary artery and late filling of the anomalous left coronary artery with a subsequent blush of opacification in the main pulmonary artery. Our one case in an infant with a ventricular septal defect and ductus arteriosus illustrates the need to look at the coronary arteries carefully even when another congenital heart abnormality is found, especially if the infant does poorly after operation.[5]

TREATMENT OF ANOMALOUS LEFT CORONARY ARTERY

Most of our patients required intensive and prolonged medical treatment of heart failure both before and after operation. In the two more recent patients a dopamine infusion was found especially helpful in preparing the patient for early operation. One patient remained stable without treatment; this case illustrates the variability of the condition.[4]

Househam *et al* reviewed the surgical options available.[7] They argue for a conservative approach particularly in the older infant because only one of their three infants who had reimplantation of the anomalous left coronary artery into the aorta survived. In 1981 Driscoll *et al* also argued for a conservative approach because only two of their eight patients operated on before the age of twelve months survived.[8] They advocated operation during childhood because 13 out of their 15 patients survived when operated on between 14 months and 12 years. Ligation of the anomalous left coronary artery may lead to subsequent angina, as shown by one patient in our series and others reported elsewhere,[14] or increased mortality.[8 15] If a two coronary artery system can be safely re-established from the aorta it is preferable to conservative treatment or ligation of the anomalous left coronary artery, as Arciniegas *et al* have emphasised.[15] Six of their infants and three of ours died after medical treatment. Successful reestablishment of a two coronary artery system restores the blood flow to the left ventricular myocardium immediately and more completely.[15] This result may considerably reduce mortality and morbidity and permit more complete recovery of the myocardium. The last four patients in our series, who have had an anastomosis of the anomalous left coronary artery to the aorta by the Takeuchi *et al* approach,[2] have all survived. They had an excellent result with proven patency of the anastomosed vessel on catheter restudy. Their symptoms have improved considerably and *x* ray and electrographic findings on follow up (12 months–7 years) are becoming more normal.

Anastomosis of the anomalous left coronary artery to the aorta is a major advance. It is important to seek out this rare condition to enable corrective surgery to be performed and thereby improve the mortality and long term morbidity. We do not believe that it is possible, as Driscoll *et al* suggest,[8] to identify those infants who present in cardiac failure and may survive into childhood with medical treatment from those who will succumb. An active policy seems justified.

Conclusions

Anomalous left coronary artery should be considered in any infant with congestive cardiomyopathy or apparent congenital mitral incompetence. The possibility of this anomaly is increased if ischaemic changes are noted on the electrocardiogram. Cross sectional echocardiography will certainly demonstrate a poorly contracting, dilated left ventricle. Although in some cases it is possible to show the anomalous left coronary artery arising from the main pulmonary artery just distal to the pulmonary valve, cross sectional echocardiography may also show what appears to be a "normal" origin of the left coronary artery. Good quality angiography remains essential in making a definitive diagnosis. Direct reimplantation of the anomalous left coronary artery into the aorta is likely to become the treatment of choice because it improves mortality and long term morbidity.

References

1 Keith JD. The anomalous origin of the left coronary artery from the pulmonary artery. *Br Heart J* 1959;21:149–61.
2 Takeuchi S, Imamura H, Katsumoto K, *et al.* New surgical method for repair of anomalous left coronary artery from pulmonary artery. *J Thorac Cardiovasc Surg* 1979;78:7–11.
3 Wesselhoeft H, Fawcett JS, Johnson AL. Anomalous origin of the left coronary artery from the pulmonary trunk. *Circulation* 1968;38:403–25.
4 Moodie DS, Fyfe D, Gill CC, et al. Anomalous origin of the left coronary artery from the pulmonary artery (Bland-White-Garland syndrome) in adult patients: long term follow-up after surgery. *Am Heart J* 1983;106:381–8.
5 Lurie PR. Abnormalities of the coronary vessels. In: Moss AJ, Adams FH, Emmanouilides GC, eds. *Heart disease in infants, children and adolescence.* 2nd ed. Baltimore: Williams and Wilkins, 1977:484–9.
6 Keith JD. Diseases of the coronary arteries and aorta. In: Keith JD, Rowe RD, Vlad P, eds. *Heart disease in*

infancy and childhood. New York: Macmillan, 1978:1914–9.

7 Househam KC, Human DG, Fraser CB, Joffe HS. Anomalous left coronary artery from the pulmonary artery—a therapeutic dilemma. *S Afr Med J* 1983;**63**:325–7.

8 Driscoll DJ, Nihill MR, Mullins CE, Cooley DA, McNamara DG. Management of symptomatic infants with anomalous origin of the left coronary artery from the pulmonary artery. *Am J Cardiol* 1981;**47**:642–8.

9 Gutgesell HP, Pinsky WW, De Puey EG. Thallium-201 myocardial perfusion imaging in infants and children. Value in distinguishing anomalous left coronary from congestive cardiomyopathy. *Circulation* 1980;**61**:596–9.

10 Caldwell RL, Hurwitz RA, Girod DA, Weyman AE, Feigenbaum H. Two-dimensional echocardiographic differentiation of anomalous left coronary artery from congestive cardiomyopathy. *Am Heart J* 1983;**106**:710–6.

11 Terai M, Nagai Y, Toba T. Cross-sectional echocardiographic findings of anomalous origin of left coronary artery from pulmonary artery. *Br Heart J* 1983;**50**:104–5.

12 King DH, Danford DA, Hutha JC, Gutgesell HP. Non invasive detection of anomalous origin of left main coronary artery from the pulmonary trunk by pulsed Doppler echocardiography. *Am J Cardiol* 1985;**55**: 608–9.

13 Robinson PJ, Sullivan ID, Kumpeng V, Anderson RH, Macartney FJ. Anomalous origin of the left coronary artery from the pulmonary trunk. Potential for false negative diagnosis with cross sectional echocardiography. *Br Heart J* 1984;**52**:272–7.

14 McNamara DG, El-Said G. Treatment of anomalous origin of left coronary artery from the pulmonary artery. *Eur J Cardiol* 1973;**1**:497–9.

15 Arciniegas E, Farooki ZQ, Hakimi M, Green EW. Management of anomalous left coronary artery from the pulmonary artery. *Circulation* 1980;**62** (suppl 1): 180–9.

Br Heart J 1987;58:385–92

Gallium-67 myocardial imaging for the detection of myocarditis in the acute phase of Kawasaki disease (mucocutaneous lymph node syndrome): the usefulness of single photon emission computed tomography

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SUMMARY Myocardial imaging with gallium-67 citrate was used to detect myocarditis in 46 consecutive infants and children (31 boys and 15 girls, mean age 21 months) with Kawasaki disease. In all of them planar imaging (group A) was performed at 6 hours and at 48 or 72 hours after the intravenous administration of a mean (SD) dose of gallium-67 citrate (0·07 (0·02) mCi/kg). Thirty four patients (24 boys and 10 girls, mean age 21 months) also had single photon emission computed tomography imaging (group B) soon after planar imaging. The patients had been ill for from 5 days to 16 days (mean (SD) 10·5 (2·4) days in group A and 10·6 (3·0) days in group B). The colour images obtained at 48 or 72 hours were positive in 41% of group A and in 64% of group B. Among the patients with clinically suspected myocarditis, 63% in group A and 80% in group B had positive myocardial images. Single photon emission computed tomography imaging permitted the identification of tracer in the myocardium, the pericardium only, or in the heart chambers.

Myocardial imaging with gallium-67 citrate, especially when used with single photon emission computed tomography imaging, is useful for the detection of myocarditis in the acute phase of Kawasaki disease.

Kawasaki disease (mucocutaneous lymph node syndrome) is a disease of unknown aetiology and pathogenesis that usually affects infants and children under four years of age. About 10—20% of these patients have coronary aneurysms that predispose them to sudden death from acute myocardial infarction. Most patients also have cardiovascular signs such as gallop rhythm and distant heart sounds, electrocardiographic abnormalities, and pericardial effusion; these are thought to be caused by myocarditis, pericarditis, and endocarditis.[1 2] Some histopathological studies on necropsy cases and series of endomyocardial biopsy specimens have confirmed that myocarditis is often present in the acute phase of Kawasaki disease. Because treatment of myocarditis may improve the prognosis, new diagnostic techniques are needed to detect this abnormality in infants and children with Kawasaki disease. We have evaluated the usefulness of myocardial imaging with gallium-67 citrate (especially when this radionuclide is used for single photon emission computed tomography) in the detection of myocarditis in patients with acute phase Kawasaki disease.

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Patients and methods

Patients—We examined 46 consecutive patients with Kawasaki disease (31 boys and 15 girls, age range 6 months to 5 years and 11 months, mean 1 year and 9 months) who were admitted to the Toho University hospital from July 1985 to March 1986. In all of these patients clinical diagnosis was based on the criteria set by the Mucocutaneous Lymph Node Syndrome Research Committee of the Ministry of Health and Welfare of Japan in 1984.[3]

Methods—In the acute phase (the illness had lasted from 5 days to 16 days; mean (SD) 10·5 (2·4) days) 0·5–1·0 mCi of gallium-67 citrate (mean (SD) 0·07 (0·02) mCi/kg) was administered intravenously; the amount administered depended on the child's body weight. Planar imaging was performed in the anterior and in the 45° left anterior oblique projections in all 46 patients (group A) 6 hours and 48 or 72 hours after injection of the tracer. Soon after planar imaging 34 patients were also examined by single photon emission computed tomography imaging (group B); the gamma camera was rotated around the patient from the 40° right anterior to the 50° left posterior projections. These 180° were divided into 32 equal angles; 6 hours after injection of the tracer 30 seconds per angle and 48 or 72 hours afterwards 50 seconds per angle were required for imaging. Both planar and single photon emission computed tomography imaging were performed with a ZLC 7500 gamma camera, Shimazu Inc., using medium energy, high sensitivity collimator. The data obtained were recorded and analysed to make colour images by computer (Scintipac 2400, Shimazu Inc.).

Three paediatric cardiologists classified the colour images of the anterior view in planar imaging and of the transverse plane view against the truncal axis in single photon emission computed tomography imaging at 48 or 72 hours into four grades. Each was unaware of the clinical data of the patients and of the judgements made by the other two.

The four grades were: negative (−), heart not identified; positive 1+, showing a vague silhouette of the heart in planar imaging or a vague or incomplete outline of the ventricular walls by single photon emission computed tomography imaging;

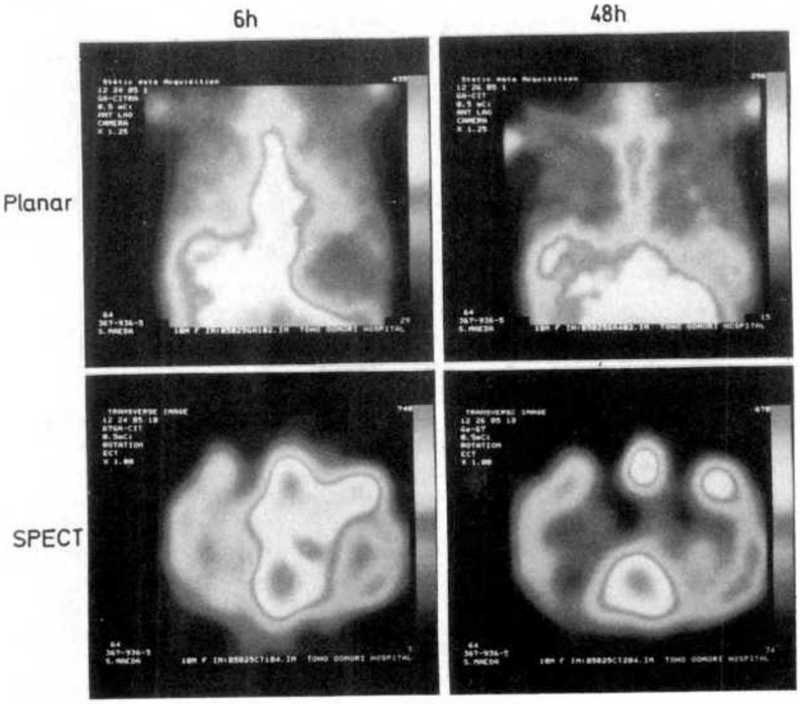

Fig 1 *Planar and single photon emission computed tomographic (SPECT) images of a typical negative case. There was a remarkable accumulation of gallium-67 (see cardiac silhouette) in the planar image at 6 hours (top left). Gallium-67 was localised both in the ventricular cavity and in the myocardium in the SPECT image (bottom left). No accumulation of gallium-67 in the heart was seen in planar or SPECT images at 48 hours (top right and bottom right).*

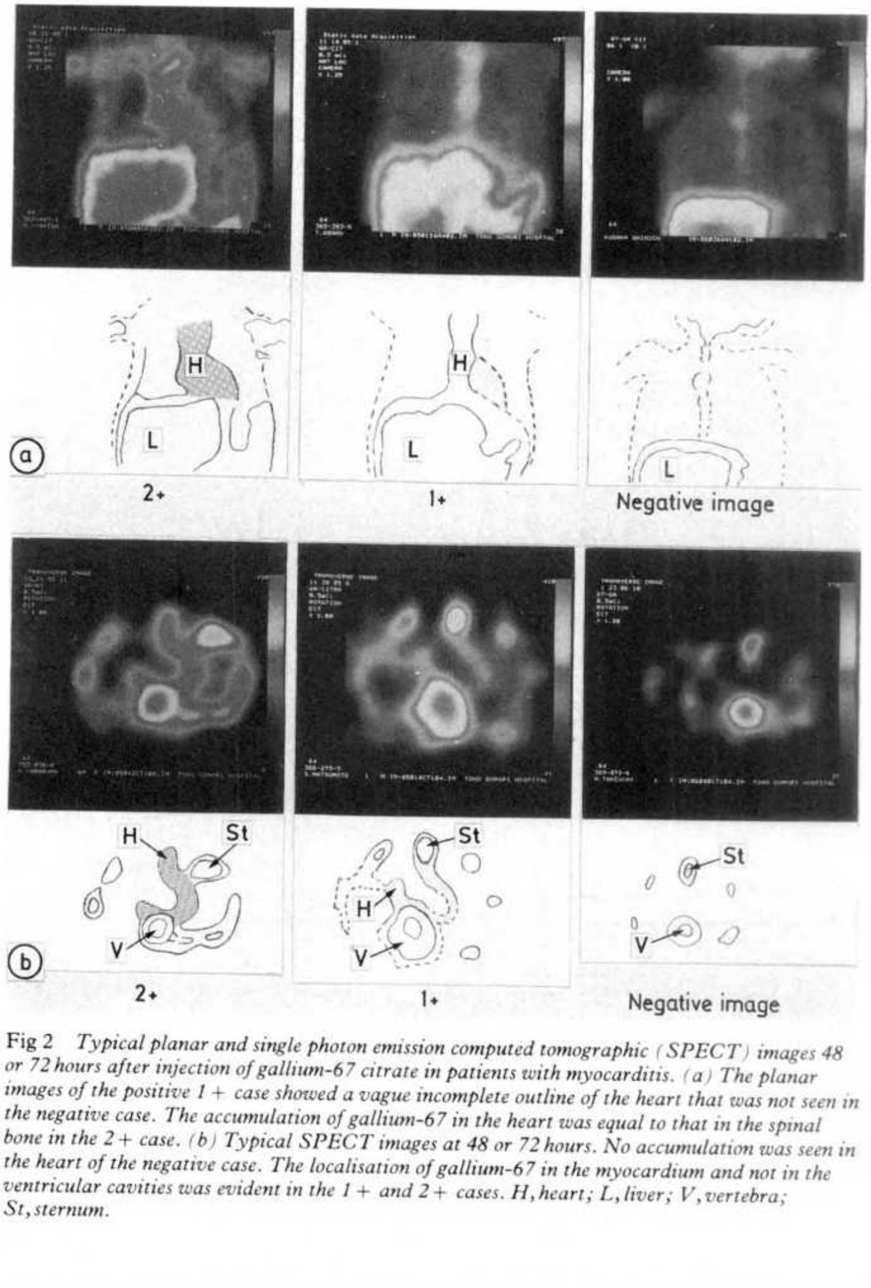

Fig 2 *Typical planar and single photon emission computed tomographic (SPECT) images 48 or 72 hours after injection of gallium-67 citrate in patients with myocarditis. (a) The planar images of the positive 1+ case showed a vague incomplete outline of the heart that was not seen in the negative case. The accumulation of gallium-67 in the heart was equal to that in the spinal bone in the 2+ case. (b) Typical SPECT images at 48 or 72 hours. No accumulation was seen in the heart of the negative case. The localisation of gallium-67 in the myocardium and not in the ventricular cavities was evident in the 1+ and 2+ cases. H, heart; L, liver; V, vertebra; St, sternum.*

positive 2+, showing an obvious silhouette of the heart by planar imaging, or clear identification of the ventricular walls by single photon emission computed tomography imaging; positive 3+, a greater accumulation of radionuclide in the heart than in the spinal bone.

In the event of disagreement among the three physicians, we used the grade agreed upon by two cardiologists or the mean of the three different grades.

While patients were in hospital the following were measured at least twice a week: complete blood counts, serum total protein and albumin, erythrocyte sedimentation rates, C-reactive protein, and creatine kinase MB expressed as a fraction of total creatine kinase. The cardiothoracic ratio on chest

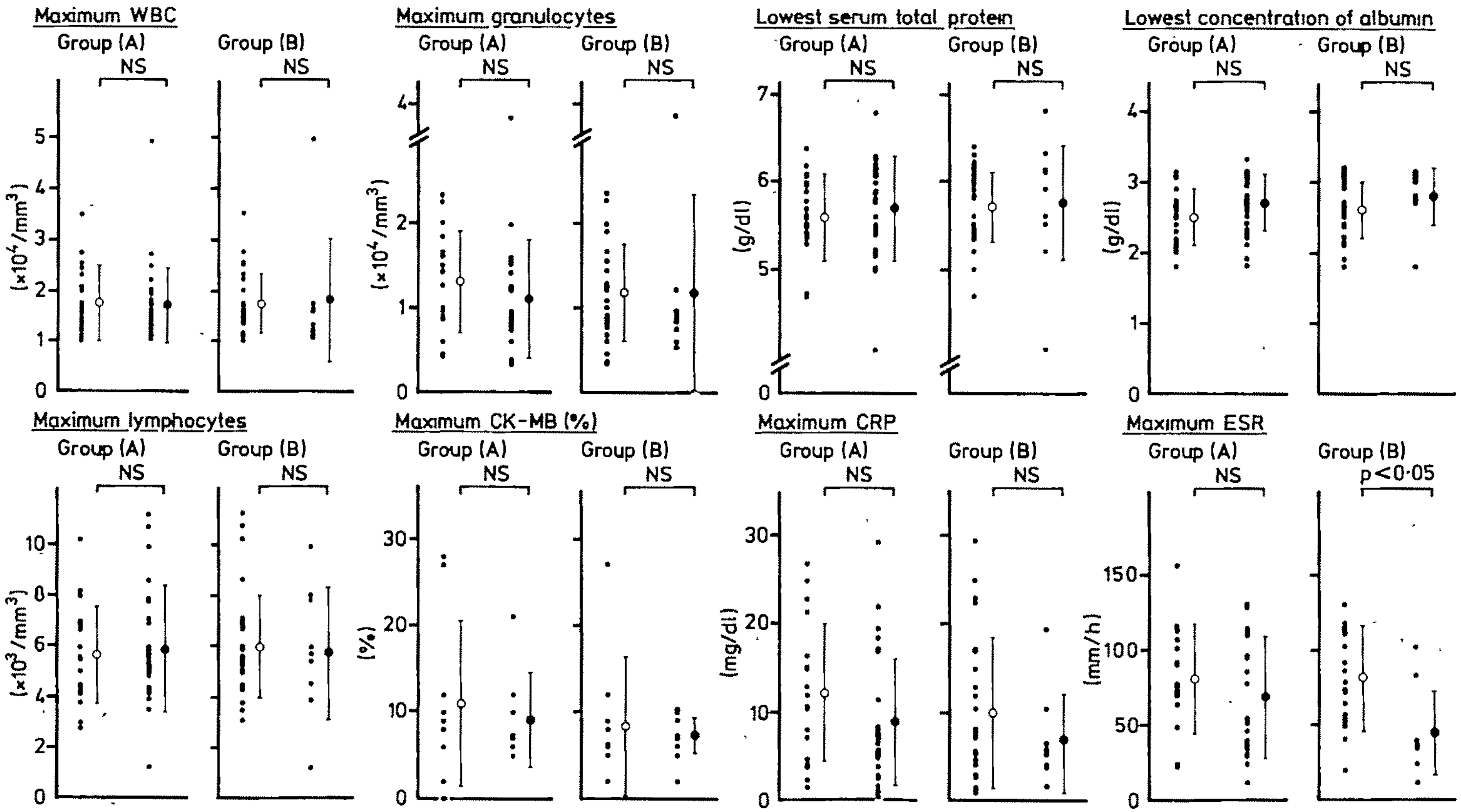

Fig 3 *A comparison of laboratory data in the positive and negative cases by planar (A) and single photon emission computed tomographic (SPECT) imaging (B). WBC, white blood cells, CK-MB (%), MB fraction of total serum creatine kinase; CRP, C reactive protein; ESR, erythrocyte sedimentation rates. The highest ESRs in group B were significantly higher in the positive cases than in the negative cases (in the positive cases mean (SD) 79·4 (30·6), n = 20 and in the negative cases mean (SD) 46·6 (30·9), n = 7, p < 0·05). There were no significant differences for the other laboratory data between patients with positive and negative images.*

x ray films and the electrocardiograms and echocardiograms were examined at least once a week. When there was an increase or reduction of at least 5% in the cardiothoracic ratio on the chest *x* ray films during the clinical course cardiomegaly or the regression of cardiomegaly was diagnosed. Electrocardiograms were analysed by the criteria of Yoshitake *et al*[4] for cardiac rhythm, PQ intervals, corrected QT intervals, significant changes in the voltage of R waves, and ST-T changes. Coronary aneurysms, pericardial effusion, and valve insufficiency were detected by M mode and cross sectional echocardiography and cross sectional colour Doppler echocardiography. We compared these findings and abnormalities in heart sounds (that is distant heart sounds and gallop rhythm) with the results of myocardial imaging with gallium-67.

Results

MYOCARDIAL IMAGING WITH GALLIUM-67

Figure 1 shows both planar and single photon emission computed tomography images in a typical case. At 6 hours there was a remarkable accumulation of gallium-67 in the cardiac silhouette in planar imaging. The single photon emission computed tomography image at 6 hours shows that gallium-67 has accumulated both in the blood in the ventricular cavity and in the myocardium. At 48 hours neither planar nor single photon emission computed tomography imaging showed accumulation of gallium-67 in the heart. The planar image of a 1+ positive case (fig 2a) shows a vague outline of the heart which was not seen in the negative case. There was a remarkable accumulation of gallium-67 in the heart in the 2+ positive case. In positive cases single photon emission computed tomography imaging showed accumulation of the tracer in the myocardium, but not in the blood in the ventricular cavities.

In group A 19 patients (41%) had positive images (12 cases were 1+ and 7 cases were 2+) and in group B 25 patients (64%) had positive images (15 cases were 1+ and 10 cases were 2+). No patient from either group was graded as 3+. The frequencies of positive cases in male and female patients were 65% and 53% in group A and 80% and 56% in group B respectively. There was no significant sex-related difference in the percentages of positive cases. Six positive cases in group B were re-examined at the time of discharge and one case remained positive. A month later this case was negative.

Laboratory data—Figure 3 shows a comparison between positive and negative cases in groups A and B. In the acute phase the maximum percentage of the MB fraction of creatine kinase was slightly higher in the positive cases than in the negative cases in both groups but not significantly. In group B the maximum erythrocyte sedimentation rate was significantly higher in the positive cases than in the negative cases (79·4 (30·6) *vs* 46 6 (30·9) mm/h, $p < 0{\cdot}05$). There were no other significant differences in other laboratory data between the positive and negative cases in either group A or B (fig 3).

A COMPARISON OF GALLIUM-67 MYOCARDIAL IMAGING AND CLINICAL FINDINGS IN GROUPS A AND B (TABLES 1 AND 2)

Clinical signs—None of the patients had congestive heart failure. Abnormal heart sounds were noted in 41% (19/46) in group A and 38% (13/34) in group B. Positive images were obtained in 8 (42%) cases out of the 19 cases with abnormal heart sounds in group A while 9 (69%) cases out of the 13 cases with abnormal heart sounds in group B showed positive images.

Electrocardiograms—Serial electrocardiograms revealed abnormalities in 43% (20/46) patients in group A and 47% (16/34) in group B. Of those cases with abnormal electrocardiograms, 12 (60%) out of 20 showed positive planar images and 13 (81%) out of 16 showed positive single photon emission computed tomography images.

Chest x rays—Only 25 cases in group A and 15 cases in group B had chest *x* rays that were suitable for reliable assessment of cardiomegaly. In the remain-

Table 1 *Correlation of planar images with clinical signs*

	Abnormal findings			
Planar images	*Heart sounds*	*Cardiomegaly*	*ECG*	*Echocardiography*
Abnormality	19/46 (41%)	4/25 (16%)	20/46 (43%)	24/46 (52%)
Positive 1+	6/19 (32%)	1/4 (25%)	9/20 (45%)	10/24 (42%)
Positive 2+	2/19 (11%)	1/4 (25%)	3/20 (15%)	2/24 (8%)
Negative	11/19 (57%)	2/4 (50%)	8/20 (40%)	12/24 (50%)

Nineteen of these 46 cases had two or more abnormal findings in the above four examinations and 12 cases (63%) out of the 19 had positive images.

Table 2 *Correlation of single photon emission computed tomography (SPECT) images with clinical signs*

	Abnormal findings			
SPECT images	*Heart sounds*	*Cardiomegaly*	*ECG*	*Echocardiography*
Abnormality	13/34 (38%)	2/15 (13%)	16/34 (47%)	18/34 (53%)
Positive 1+	5/13 (38%)	1/2 (50%)	7/16 (43%)	9/18 (50%)
Positive 2+	4/13 (31%)	0/2 (0%)	6/16 (38%)	4/18 (22%)
Negative	4/13 (31%)	1/2 (50%)	3/16 (19%)	5/18 (28%)

Fifteen of these 34 cases had two or more abnormal findings in the above four examinations and 12 cases (80%) out of the 15 had positive images

der the *x* rays were unsatisfactory (for example because of a mismatch of the respiratory phase or rotation of the trunk). Cardiomegaly was present in 16% (4/25) in group A and 13% (2/15) in group B, and half the patients in groups A and B showed positive gallium-67 myocardial images.

Echocardiography—Fifty two per cent (24/46) of group A and 53% (18/34) of group B had abnormal echocardiograms (that is transient pericardial effusion, persistent aneurysms or dilatation of coronary arteries, and transient aortic valve insufficiency). Of these, 50% (12/24) in group A and 72% (13/18) in group B showed positive images by gallium-67 myocardial imaging. The only patient who had transient pericardial effusion, transient aortic valve insufficiency, and persistent coronary aneurysms was classified as positive (1+) by planar imaging; single photon emission computed tomography imaging was not performed in this patient. Five cases in group A, including this case, had aneurysms or appreciable dilatation of coronary arteries at discharge and three (60%) of them had positive images. In group B four cases had coronary aneurysms or dilatation and all of them showed positive images.

Cases which had two or more abnormal findings in the above four examinations were said to have clinically suspected myocarditis; in group A 12 (63%) out of 19 cases with clinically suspected myocarditis showed positive images while 12 (80%) out of 15 such cases in group B showed positive images.

Discussion

Infants and children with Kawasaki disease in the acute phase often have abnormal findings such as gallop rhythm and distant heart sounds, prolonged PQ intervals and QTc, as well as echocardiographic evidence of pericardial effusion and valve insufficiency; all of these abnormalities are thought to be due to pancarditis.[1 2] Some histopathological studies of specimens obtained by endomyocardial biopsy[1 5] have also suggested that the myocardium is often inflamed in the acute phase. Fujiwara and Hamashima classified cardiac lesions into four stages according to the duration of illness at death.[6] All those who died in the acute phase, especially those in stage 1 (duration of illness to death was 0 to 9 days), showed considerable infiltration of polymorphonuclear leucocytes and lymphocytes into the myocardium. There are also reports of sudden death caused by extension of inflammation to the cardiac conduction systems.[7] In Kawasaki disease the progression to myocardial fibrosis and hypertrophy from myocarditis is suspected.[5] Apart from cardiac biopsy conventional investigations are not very helpful in detecting myocarditis and in assessing its severity in patients with abnormal clinical signs. This is mainly because the cardiac symptoms in Kawasaki disease are usually mild and the clinical course is not like that of typical infectious myocarditis. For example changes in electrocardiograms are so mild that only serial tracings reveal faint abnormalities,[4] and creatine phosphokinase and the MB fraction are increased in only a few cases.[8]

Gallium-67 has a half life of 78 hours and produces four gamma rays with energies suitable for scanning. There is no beta emission, and the radiation dose to the patient is well within the acceptable range.[9] Recently gallium-67 citrate imaging was reported to be useful in the detection of clinical and experimental myocarditis, pericarditis, and endocarditis.[9 10] Most of the cases reported were the subject of individual case reports and a few workers have reported small series.[10]

The uptake of gallium-67 by the acute inflammatory lesions is thought to occur in three ways. The most important and best studied one is the role of polymorphonuclear leucocytes. The other two ways are via lymphocytes and the so-called "non-cellular pathway"[11 12]; both these routes have been proposed as mechanisms of accumulation in states such as agranulocytosis. Gallium-67 resembles the ferric ion in its atomic radius, charges, and in the types of inorganic complexes that it forms; so gallium-67 binds to iron-binding molecules and cells—for example lactoferrin, transferrin, ferritin, and siderophores.[13] The lysosomes of polymorphonuclear leucocytes are rich in lactoferrin and several investigations suggest that lysosomal binding is important in the localisation of gallium-67 within inflammatory lesions.[12–14] After accumulating at sites of inflammation leucocytes discharge some of the content of the lysosomes, including lactoferrin. The discharged lactoferrin tends to remain on the receptor sites in tissue macrophages and lymphocytes.[13]

In the acute phase of Kawasaki disease patients show considerable increases in numbers of immature polymorphonuclear leucocytes. The kinetics of lactoferrin have not been studied in patients with Kawasaki disease, but the activity of the enzyme, β glucuronidase, released from the lysosomes of polymorphonuclear leucocytes is significantly higher in the acute phase than in the recovery phase.[15] Characteristic cardiac abnormalities in the acute phase of Kawasaki disease are acute perivasculitis and vasculitis of microvessels and small arteries. Acute pericarditis, interstitial myocarditis, and endocarditis are also seen; the myocarditis is characterised by oedema and infiltrating cells consisting of polymorphonuclear leucocytes and lymphocytes.[6] At the earliest stage polymorphonuclear leucocytes predominate; and these are rapidly replaced by lymphocytes.[16] Even biopsy specimens obtained early in the recovery phase contain lymphocytes, plasma cells, histiocytes, and some mast cells rather than polymorphonuclear leucocytes.[5]

These mechanisms for the accumulation of gallium-67 in inflammatory lesions raise the possibility of using gallium-67 citrate to detect myocarditis as a complication of the acute phase of Kawasaki disease. Ito *et al* and Sty *et al* reported some positive cases in planar imaging by gallium-67 citrate in patients with Kawasaki disease, but they did not study the corresponding clinical features in these patients.[17 18] We believe that polymorphonuclear leucocytes and lactoferrin were responsible for producing the positive images in our series in the acute phase. Lymphocytes or the "noncellular pathway" or both may have been responsible for the positive image at discharge that was found in one patient.

Although the most typical appearance of pericarditis in gallium-67 imaging was a "hot" rim of uneven thickness surrounding the periphery of the entire heart in planar imaging, diffuse, faint activity in the cardiac silhouette has been seen in some cases.[19] Single photon emission computed tomography imaging was useful because it showed the localisation of gallium-67 in the myocardium as well as in the pericardium of the positive cases. Moreover, this technique showed that the positive images were not the result of high gallium-67 counts in the systemic circulation; this was established by comparing the images at 6 hours with those at 48 or 72 hours in group B. Single photon emission computed tomography imaging was also better than planar imaging; it was more sensitive (80% in group B *vs* 63% in group A), although this difference was not statistically significant. Single photon emission computed tomography requires more expensive equipment and a longer recording time than planar imaging.

References

1 Onouchi Z, Tomizawa N, Goto M, Nakata K, Fukuda M, Goto M. Cardiac involvement and prognosis in acute mucocutaneous lymph node syndrome. *Chest* 1975;**68**:297–301.

2 Nakano H, Ueda K, Sato A, Tsuchitani Y. Doppler detection of tricuspid regurgitation following Kawasaki disease. *Pediatr Radiol* 1986;**16**:123–5.

3 Kawasaki T. Agreement with the guidelines by the Mucocutaneous Lymph Node Syndrome Research Committee [In Japanese]. *Nippon Shonikagakkai Zasshi* 1984;**88**:2693.

4 Yoshitake K, Naganuma M, Koike K, *et al.* Electrocardiographic findings in MCLS. [In Japanese]. *Iryo* 1980;**34**:24–7.

5 Yutani C, Go S, Kamiya T, *et al.* Cardiac biopsy of Kawasaki disease. *Arch Pathol Lab Med* 1981;**105**:470–3.

6 Fujiwara H, Hamashima Y. Pathology of the heart in Kawasaki disease. *Pediatrics* 1978;**61**:100–7.

7 Fujiwara H, Kawai C, Hamashima Y. Clinicopathologic study of the conduction systems in 10 patients with Kawasaki's disease (mucocutaneous lymph node syndrome). *Am Heart J* 1978;**96**:744–50.

8 Yamamoto S, Umezawa T, Hashiguchi R, Saji T, Matsuo N. Serum creatine kinase in Kawasaki disease [In Japanese]. *Shonika Rinsho* 1985;**38**:2312–6.

9 Reeves WC, Jackson GL, Flickinger FW, *et al.* Radionuclide imaging of experimental myocarditis. *Circulation* 1981;**63**:640–4.

10 Taillefer R, Dionne D. Gallium-67 uptake by the heart. *Semin Nucl Med* 1983;**13**:176–8

11 Merz T, Malmud L, McKusick K, Wagner HN. The mechanism of the Ga-67 association with lymphocytes. *Cancer Res* 1974;**34**:2495–9.

12 Dhawan VM, Sziklas JJ, Spencer RP. Localization of Ga-67 in inflammations in the absence of circulating polymorphonuclear leukocytes. *J Nucl Med* 1978;**19**:292–4.

13 Hoffer P. Gallium: mechanisms. *J Nucl Med* 1980;**21**:282–5.

14 Gelrud LG, Arseneau JC, Milder MS, *et al.* The kinetics of gallium-67 incorporation into inflammatory lesions: experimental and clinical studies. *J Lab Clin Med* 1974;**63**:489–95.

15 Niwa Y, Sohmiya K. Enhanced neutrophilic functions

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Prediction of outcome in dilated cardiomyopathy

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SUMMARY One hundred and sixty nine patients (mean age 39·1 years) with documented dilated cardiomyopathy were studied for a mean of 5·5 years One hundred and four patients died during this period. The average (SD) interval from the onset of symptoms to death was 4·1 (3·7) years. One year and five year mortality rates were 27·8% and 57·4% respectively. Most of the deaths occurred within two years of diagnosis. The only difference between survivors and those who died was in the severity of left ventricular dysfunction at the time of referral. Significant differences between survivors and non-survivors were found for left ventricular end diastolic pressure (17·3 versus 23·4 mm Hg), left ventricular end systolic volume (87·4 versus 128·9 ml/m^2), left ventricular end diastolic volume (130·7 versus 173·2 ml/m^2), and ejection fraction (32·8 versus 25·4%). The duration of previous symptoms, preceding virus infection, positive family history, recent pregnancy, or heavy alcohol intake did not seem to influence prognosis. Nor did treatment, which was similar in both groups with a quarter of the patients receiving vasodilators.

Patients with dilated cardiomyopathy have a high mortality irrespective of treatment. The only identifiable prognostic indicator was the severity of left ventricular impairment at referral.

Dilated cardiomyopathy is a heart muscle disease of unknown cause in which one or both ventricles are dilated and poorly contracting.[1-3] Various clinical, radiological, angiographic, haemodynamic, and histopathological variables have been suggested as predictors of outcome in dilated cardiomyopathy, but there is no uniform agreement about their usefulness.[4-6]

One year mortality in this condition may vary from 31% to 35%[4 6 7] and five year mortality has been reported to be around 50%.[7-9] This poor prognosis seems not to have been modified during the past two decades, despite the introduction of new diuretics and the use of vasodilators and anticoagulants during this period.

To strengthen understanding of the clinical course of this disorder we report experience at Hammersmith Hospital in the diagnosis, treatment, and follow up of these patients. To our knowledge this is the largest series of patients with well documented dilated cardiomyopathy so far reported and the observations are relevant to the selection of patients for cardiac transplantation and the timing of the operation.

Patients and methods

We retrospectively analysed data on 209 consecutive patients with dilated cardiomyopathy who were first seen in the Clinical Cardiology Unit (Department of Medicine) at Hammersmith Hospital from March 1962 to March 1982. Only 169 patients were included in the study. Eighteen patients were excluded because data were incomplete and twenty two were excluded because they had predominant or exclusive dilatation of the right ventricle. Most patients were referred for the evaluation of cardiac failure. All patients were followed up in the outpatient department. The follow up period was defined as the interval from the date of first admission to Hammersmith Hospital until either death or 31 March 1983. The interval from the onset of symptoms to the first admission was also analysed. There were 131 men and 38 women. One hundred and thirty eight patients were European, 17 were black, and 14 were Asian.

Dilated cardiomyopathy was identified as a heart muscle disease of unknown cause with dilatation of the left or right heart or both[1-3]; so the diagnosis

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was made by exclusion of other causes of cardiac failure. Exclusion criteria included: heart muscle disease of known origin (for example amyloid, sarcoid, haemochromatosis), clinical or angiographic coronary heart disease or both (patients with obstruction of $\geqslant 50\%$ of one or more major coronary artery branches or who had considerable irregularity of one or more vessels were excluded even if it was thought that the left ventricular failure could not be attributed to the coronary disease shown on angiography), systemic hypertension, and hypertrophic cardiomyopathy. The diagnosis required a left ventricular ejection fraction of $<45\%$ and usually included also: (*a*) a history of dyspnoea on exertion or at rest; (*b*) physical signs of left or right heart failure or both; (*c*) cardiomegaly on chest *x* ray; (*d*) one or more of the following electrocardiographic abnormalities—atrial fibrillation or atrial flutter, conduction system disturbances, and evidence of a left ventricular disorder usually with high voltage in the chest leads and repolarisation abnormalities; (*e*) left ventricular end diastolic pressure > 15 mm Hg.

The symptomatic state was classified according to the New York Heart Association classification. Death was defined as sudden when it was unexpected and occurred within 24 hours of the onset of new symptoms. Complex ventricular arrhythmia was defined as the presence of multiform or repetitive ventricular extrasystoles (couplets or bursts of ventricular tachycardia) or both.

To evaluate possible risk factors we analysed alcohol intake, recent pregnancy, family history and febrile illness heralding the onset of symptoms, and positive anti-viral titres.

MEASUREMENTS

All patients had a baseline 12 lead electrocardiogram and chest *x* ray. R waves in the left precordial lead V5 over 20 mV were considered as high voltage and under 5 mV as low voltage. Ambulant electrocardiogram monitoring was carried out in all patients seen after 1980—57% of the total series. Blood samples were also taken to measure serum iron, antinuclear factor, thyroid function, rheumatoid factor, and virus antibody titres.

HAEMODYNAMIC AND ANGIOGRAPHIC STUDIES

All patients underwent cardiac catheterisation by the percutaneous approach through the femoral or brachial artery. Left and right heart pressures were recorded with an Electronics for Medicine DR8 recorder. Fluid filled lines and P23D Statham transducers were used. The mid chest was used as a reference point for the calibration of zero.

Left ventricular volumes were determined by Grant *et al's* method[10] from the biplane anteroposterior and lateral projections filmed at 30 frames/s after the injection of contrast material into the left ventricle. The ejection fraction (EF) was calculated by the formula: EF = (LVEDV − LVESV)/LVEDV, where LVESV = left ventricular end systolic volume and LVEDV = left ventricular end diastolic volume. Volumes are given as millilitres per square metre of body surface area (ml/m^2). Ninety seven (57%) of the patients underwent coronary angiography. This includes all patients studied since 1980 irrespective of age. Those who did not have angiography had no clinical, electrocardiographic, or ventriculographic features of coronary heart disease and none who came to necropsy had clinically significant coronary atheroma. Thirty two (18·8%) patients underwent percutaneous right ventricular endomyocardial biopsy. Biopsy was used to identify myocarditis and the specific heart muscle diseases.[11] All endomyocardial biopsy specimens in the current series showed nonspecific morphological abnormalities and there was no evidence of active or past myocarditis. Since March 1983 we have performed myocardial biopsies on 39 more patients with clinically similar dilated cardiomyopathy, 21 of whom were reported as showing features of active past or healing myocarditis on biopsy.

Echocardiographic and radionuclide measurements were not included in this analysis because they only became available after the series was started.

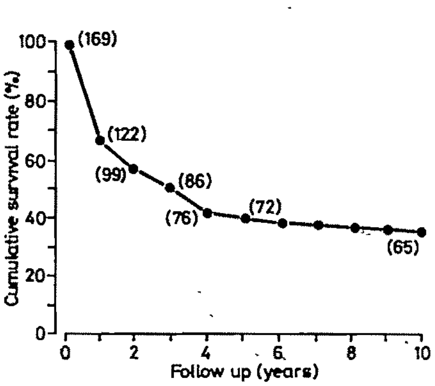

Fig 1 *10 year survival curve of 169 patients with dilated cardiomyopathy. Numbers in parentheses are patients alive at the beginning of interval. Numbers at years 6, 7, 8, and 9 were omitted because of the small amount of attrition between 5 and 10 years.*

TREATMENT

All patients were taking diuretics. Digitalis preparations were not used routinely in patients in sinus rhythm. Anticoagulant drugs are normally prescribed when dilated cardiomyopathy is diagnosed, irrespective of the cardiac rhythm. One quarter of the patients received vasodilator drugs.

STATISTICAL ANALYSIS

The data were stored in a computer and analysed by the statistical package, Minitab. The probability of survival from the time of first evaluation at Hammersmith Hospital was analysed by the life table method. The t test and χ^2 test were used to analyse significance of univariate prognostic factors. Linear regression analysis was carried out to test the relation between clinical or haemodynamic variables and the duration of survival in those who died. Results were considered to be statistically significant when $p < 0{\cdot}05$.

Results

One hundred and sixty nine patients with documented dilated cardiomyopathy were studied. The mean (SD) age at the onset of symptoms was 39·1 (14·1) years. The interval from the onset of symptoms to first evaluation at Hammersmith Hospital was 1·8 (2·8) years. The average duration from the onset of symptoms to death was 4·1 (3·7 years). The mean follow up period was 5·5 (4·2) years. Patients who survived five years were unlikely to die thereafter (fig 1).

CLINICAL CHARACTERISTICS

Table 1 summarises the clinical symptoms and physical signs found on the first admission to Hammersmith Hospital. The commonest symptom was dyspnoea either on exertion or at rest (85·8%) followed by palpitation and oedema. Chest pain was not uncommon and it was present in 35 patients (20·7%), all of whom underwent coronary angiography which excluded clinically significant coronary artery disease as defined earlier. A mitral regurgitant murmur was present in 37·9% of the patients. Pulmonary or systemic embolism had occurred in 10·6% and 8·3% respectively before referral to Hammersmith. Atrial fibrillation was present in only 23·7% of those patients who had had embolic events. Asymptomatic cardiomegaly was the first manifestation of illness in eight (4·7%) patients.

All patients had radiographic evidence of cardiomegaly and the average cardiothoracic index was 58·8 (6·8%).

Table 1 *Clinical characteristics of patients with dilated cardiomyopathy*

Feature	*No*	*%*
Dyspnoea	145	85·8
Third heart sound	145	85·8
MR murmur	64	37·9
Palpitation	50	29·6
Oedema	49	28·9
Chest pain	35	20·7
Pulmonary emboli	17	10·6
Systemic emboli	14	8·3

MR, mitral regurgitation

Table 2 *Electrocardiographic features of patients with dilated cardiomyopathy*

Feature	*No*	*%*
Sinus rhythm	129	76·3
Atrial fibrillation	34	20·1
LBBB	35	20·7
RBBB	7	4·1
VE isolated	43	25·4
VE complex	25	14·8
High voltage V5	54	34·4
Low voltage V5	5	3·2
LA enlargement	76	44·9

LBBB, left bundle branch block; RBBB, right bundle branch block; VE, ventricular extrasystoles, LA, left atrium.

Table 2 shows electrocardiographic features. Atrial fibrillation and ventricular extrasystoles were the commonest arrhythmias present in this series. Complex ventricular arrhythmias were present in 14·8% of the patients. Complete left bundle branch block was the commonest conduction system defect (20·7%). Right bundle branch block was rarely present (4·1%). High voltages (>20 mV) in the left precordial lead V5 occurred in 34·4% of the cases while low voltages (<5 mV) were occasionally seen (3·2%). Arrhythmias were documented by routine Holter recording in 97 patients investigated after 1980. Before that date, complex ventricular arrhythmias or ventricular tachycardia were only found by chance recording or when they caused symptoms.

HAEMODYNAMIC FEATURES

Table 3 shows the baseline haemodynamic findings. The left ventricular end diastolic pressure was raised (20·8 (9·8) mm Hg) and the ejection fraction was reduced (29·2 (12·7)%). Both the left ventricular end systolic volume (104·7 (57·1) ml/m^2) and the end diastolic volume (148·4 (64·2) ml/m^2) were increased. The mean stroke volume (42·1 (22·5) ml/m^2) was at the lower limit of normal but there was wide variation.

The left ventricular angiograms showed a markedly dilated and poorly contracting left ventricle in all patients, with mitral regurgitation ranging from 0 to moderate (grade 2 out of 4).

During the period of analysis 104 of the 169 patients died. Nearly all deaths were cardiac in origin

Table 3 *Haemodynamic and angiographic variables of patients with dilated cardiomyopathy*

Variable	*Mean (SD)*	*Normal value*
LVEDP (mm Hg)	20·8 (9·8)	< 12
LVESV (ml/m^2)	104·7 (57·1)	21–34
LVEDV (ml/m^2)	148·4 (64·2)	64–96
SV (ml/m^2)	42·1 (22·5)	43–62
EF (%)	29·2 (12·7)	63–72

LVEDP, left ventricular end diastolic pressure, LVESV, left ventricular end systolic volume, LVEDV, left ventricular end diastolic volume; SV, stroke volume; EF, ejection fraction

and sudden death occurred in 8·6% of the cases. Figure 1 shows the cumulative survival rates. The survival curve shows a one year survival rate of 72·2%. Five year survival was 42·6%. Most of the deaths occurred during the first two years of follow up (41·4%).

In order to determine whether there were differences between patients who were still alive (survivors) and those who were dead (non-survivors) at the end of the analysis period we compared the baseline clinical, serological (virus), electrocardiographic, radiographic, and haemodynamic variables of both groups. No significance differences were found either in the clinical or in the electrocardiographic variables between survivors and non-survivors nor any difference in the cardiothoracic ratio (table 4). The only significant differences between survivors and non-survivors were with the haemodynamic and angiographic variables shown in table 5. Those who died had higher left ventricular end diastolic pressure than did the survivors (23·4 versus 17·3 mm Hg; $p < 0·001$). They also had lower ejection fractions (25·4 versus 32·8%; $p < 0·005$) and larger left ventricular end systolic volumes (128·9 versus 87·4 ml/m^2; $p < 0·01$) and left ventricular end diastolic volumes (173·2 versus 130·7 ml/m^2; $p < 0·01$) than did the survivors. The stroke volume was similar in both groups (43·2 versus 40·6 ml/m^2; p NS).

Linear regression analysis between the clinical, electrocardiographic, radiographic, haemodynamic, and angiographic variables and the length of survival in those who died showed a relation only with left ventricular end diastolic pressure, which was inversely correlated with duration of survival (fig 2).

Table 4 *Comparison of clinical, electrocardiographic, and radiological variables (mean (SD)) in survivors and those who died*

	Survivors	*Died*	*p*
Patients (No)	67	102	NS
Age (yr)	42·4 (13·1)	37·0 (14·4)	NS
LA enlargement (mm)	55·7 (7·2)	57·9 (6·2)	NS
Atrial fibrillation (No)	28/67	48/102	NS
VPB complex (No)	16/67	18/102	NS
LBBB (No)	14/67	22/102	NS
Embolism (No)	10/67	21/102	NS

See table 2 for abbreviations.

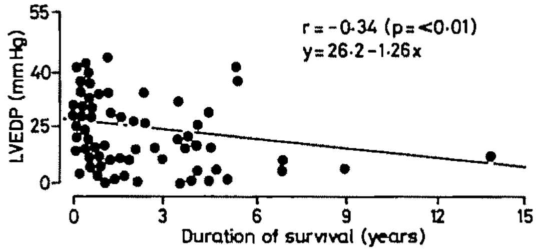

Fig 2 *Relation between left ventricular end diastolic pressure (LVEDP) and duration of survival in 65 patients who died. Most patients died within three years of referral and most of those who survived longer had lower LVEDP, although there are notable exceptions. (There is no linear correlation between the value of LVEDP and duration of survival.)*

Furthermore, we also compared 24 patients (14·2%) in whom the first manifestation of illness was not cardiac failure (for example arrhythmias, embolism, asymptomatic cardiomegaly) with 145 patients (85·8%) in whom cardiac failure was the mode of presentation. There were no significant differences in mortality and length of survival (table 6).

The presence of "risk factors" such as family history, recent pregnancy, preceding virus infection, or heavy alcohol consumption did not seem to influence prognosis. All patients were advised against taking alcohol but the effect on left ventricular function and prognosis of stopping drinking could not be analysed because there were no apparent or admitted heavy drinkers in the series who could be shown to have stopped drinking and no dramatic improvements among them. At the last follow up visit the symptomatic state according to the New York Heart Association classification was significantly better in survivors than it was in non-survivors (table 7). The clinical state had deteriorated before death in half of those who died (47·6%) compared with only 14% of

Table 5 *Comparison of haemodynamic and angiographic variables (Mean (SD)) in survivors and those who died*

Variable	*Survived*	*Died*	*p*
LVEDP (mm Hg)	17·3 (7·8)	23·4 (9·3)	< 0·001
LVESV (ml/m^2)	87·4 (58·6)	128·9 (45·8)	< 0·01
LVEDV (ml/m^2)	130·7 (66·7)	173·2 (52·9)	< 0·01
EF (%)	32·8 (11·6)	25·4 (12·8)	< 0·005

See table 3 for abbreviations

Table 6 *Duration of survival and number of deaths according to first manifestation of illness in 169 patients with dilated cardiomyopathy*

	Heart failure	*Other*	*p*
Deaths (No)	88/145	14/24	NS
Survival (yr)	2·2 (2·4)	2·6 (3·8)	NS

Table 7 *Symptomatic state at the last follow up*

NYHA	*Survivors*	*Non-survivors*
Class I or II	85·2%	30·7%
Class II or IV	14·2%	69·3%

NYHA, New York Heart Association classification.

Table 8 *Vasodilator treatment*

Variable	*No vasodilators*	*Vasodilators*	*p*
LVEDP (mm Hg)	19·5 (8·9)	22·5 (9·6)	NS
LVEDV (ml/m^2)	135·8 (53·0)	167·8 (84·8)	NS
LVESV (ml/m^2)	92·1 (41·6)	126·2 (82·0)	NS
EF (%)	30·2 (13·2)	26·9 (12·3)	NS

See table 3 for abbreviations.

the survivors—86% of the survivors were either stable or had improved their functional state. Death in 52·4% of the non-survivors was unexpected because their clinical state had not deteriorated.

All patients were taking diuretics and those in atrial fibrillation were taking digoxin. Vasodilators had been prescribed to one quarter of the patients. Patients given vasodilators had larger left ventricular end systolic and end diastolic volumes, and higher end diastolic and lower ejection fractions than those not receiving vasodilator treatment—but these differences were not significant (table 8).

Discussion

Dilated cardiomyopathy is a heart muscle disease of unknown cause.[1–3] All four cardiac chambers may be dilated[12 13] or only the left ventricle,[3 14] and rarely only the right ventricle is dilated.[15] Patients with only right ventricular dilatation were not included in this study. The commonest mode of presentation is heart failure.[5 9 16] Both shortness of breath and ventricular gallop were present in 85·8% of our patients. The clinical course is unpredictable. Most of these patients worsened quickly and died within the first two years after referral and within four years of the onset of symptoms, irrespective of the treatment used. Because we are a tertiary referral centre these figures may seem to be worse than they really are. Some of our patients referred after one to two years of treatment were undoubtedly only referred because they were deteriorating. Patients who were "doing all right", overt alcoholics, or the elderly may not have been referred. Despite this probable selection, a trend towards rapid mortality has been reported in other published series as well as ours[4 5 7] and the prognosis in this heart condition is one of the poorest. In the current series we observed a one year mortality of 27·8% and a five year mortality of over 50%. Most of our patients died within two years of the first evaluation at Hammersmith Hospital (fig 1). Conversely, patients who survived longer than this showed little tendency to die later. These were the patients who came to us despite not being on an obviously down-hill course. Their duration of symptoms before referral was similar to that in the patients who died. It is possible, indeed probable, that we are dealing with more than one disease process, but it is important to realise that a few patients with dilated cardiomyopathy can do well, with a good quality of life, and stable condition over many years even if they do not actually improve or "get better".

In several reports some clinical and haemodynamic variables have been advocated as useful predictors of the clinical course.[17–19] Years ago Hatle *et al* reported a poor outcome in those patients with both low voltages and evidence of left atrial enlargement on the electrocardiogram.[18] On the other hand, atrial fibrillation and left ventricular hypertrophy are factors considered to be associated with longevity.[6 8] Though the survivors in the current series showed a trend towards higher voltage on the electrocardiogram than those who died, the difference was not significant nor was the difference in the presence of atrial fibrillation. A favourable course has also been reported in patients who developed systemic hypertension after successful treatment for heart failure.[18] Patients in whom blood pressure rises while they are being treated for heart failure are likely to have hypertension rather than cardiomyopathy[3] and when this feature was seen in our patients we diagnosed hypertension. Recently Fuster *et al* described four factors which had predictive value in their series.[7] These were age > 55 years, cardiothoracic ratio $> 0{\cdot}55$, cardiac index $< 3{\cdot}0$ l/min/m^2, and left ventricular end diastolic pressure > 20 mm Hg. The presence of ventricular arrhythmias and conduction system defects on the electrocardiogram has been reported to be associated with bad prognosis in dilated cardiomyopathy.[19 20] Others did not observe such an association[21] nor did we in this series. Recently two studies of ventricular arrhythmias were carried out in patients with dilated cardiomyopathy by means of long term ambulatory electrocardiogram monitoring.[22 23] Huang *et al* reported that ventricular tachycardia was not predictive in their series.[22] Von Olshausen *et al* also concluded that patients at higher risk are more reliably identified by their severely impaired left ventricular function than by ventricular arrhythmias.[23] This fits in with our observation that death was rarely unexpected and rarely occurred in patients with better preserved left ventricular function. Ventricular arrhythmias were most common in those with the poorest ventricular function. In our series the only significant differences between survivors and those who died applied to haemodynamic variables. Those who died had higher left ventricular end diastolic pressure, larger end systolic and end diastolic volumes, and lower ejection fractions than the survivors; and left ventricular function overrode all other features in the prediction of prognosis (table 5). This accords with previous reports.[7 17 24] Only end diastolic pressure showed significant inverse correlation with length of survival. The higher the end diastolic pressure, the shorter the survival period tended to be (fig 2). It is interesting and important that stroke volume was not predictive. The resting cardiac output was often normal, although it failed to rise normally on effort. This was associated with a less than normal rise in rate but the poor exercise response can only be explained by a fall in stroke volume on exercise even though ventricular filling is completed rapidly. This indicates a reduciton in filling, perhaps caused by a poorer systolic contraction on exercise or a decrease in compliance. Only after a very advanced stage does the resting cardiac output fall and this is shown by Fuster's bad prognostic factors one of which was a cardiac index of $< 3{\cdot}0$, which exceeds the lower limit of normal of most laboratories.

We did not find any correlation between prognosis and febrile illness heralding the onset of symptoms, pregnancy, or excessive alcohol intake. High neutralisation titres to Coxsackie B virus were similar in survivors and those who died but in a previous report from our institution an increased frequency of high titres had been found in patients with a short history of symptoms.[25] Pulmonary and systemic embolism occurred in 10·1% and 8·3% respectively and all episodes occurred before referral to us and before the introduction of anticoagulants. These episodes had occurred irrespective of the cardiac rhythm. In fact, atrial fibrillation was only present in 23·7% of those patients who developed embolism. All patients with dilated cardiomyopathy seen at Hammersmith Hospital were given anticoagulants on diagnosis and no further embolism occurred.

All patients were on diuretics and all of those in atrial fibrillation were taking digoxin. One quarter of them were also taking vasodilator drugs. The efficacy of vasodilators in improving the haemodynamic state in these patients has already been proved[26 27] but the improvement in measured exercise capacity is disappointing. Since vasodilators tended to be given to patients with worse left ventricular function (table 8) it was not possible to evaluate statistically the effect of these drugs on prognosis but there was certainly no obvious benefit in patients with advanced disease.

Despite two decades of hard investigation of dilated cardiomyopathy, the underlying cause or causes are still unknown and no treatment is yet available to reverse pathogenesis. Only an understanding of the underlying causes will make specific treatment possible. Improvement in the prognosis of these patients will only come when this knowledge is coupled with earlier recognition. We were unable to confirm from our data the suggestion that virus myocarditis had preceded or initiated dilated cardiomyopathy but we are perplexed by the great increase in biopsy diagnosis of myocarditis since 1982.

This is the largest series of patients with dilated cardiomyopathy so far reported. Its analysis confirmed that the disorder has a high mortality irrespective of the type of treatment, and the severity of left ventricular functional impairment (at referral) appears to be the main determinant of reduced survival, possibly because by the time symptoms develop or become at all limiting, dilatation may already have reached the point at which further deterioration is inevitable. Our observations are of importance in deciding the timing of cardiac transplantation. Some patients continue to do well and are stable for many years but patients with ejection fractions below 25% and deteriorating symptoms are unlikely to survive more than two years and may die at any time.

References

1 Oakley CM. Clinical definitions and classification of the cardiomyopathies. *Postgrad Med J* 1972;48:703–13.

2 Goodwin JF, Oakley CM. The cardiomyopathies. *Br Heart J* 1972;34:545–52.

3 Oakley CM. Diagnosis and natural history of congestive (dilated) cardiomyopathy. *Postgrad Med J* 1978; 54:440–7.

4 Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983;51:831–6.

5 Segal JP, Stapleton JF, McClellan JR, Waller BF, Harvey WP. Idiopathic cardiomyopathy: clinical features, prognosis, and therapy. *Curr Probl Cardiol* 1978;3:1–48.

6 Kuhn H. Prognosis and possible presymptomatic manifestations of congestive cardiomyopathy. *Postgrad Med J* 1978;54:451–9.

7 Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Branderburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981;47:525–31.

8 Convert G, Delaye J, Beaune J, Biron A, Gonin A. Etude pronostique des myocardiopathies primitives non obstructives. *Arch Mal Coeur* 1980;3:227–37.

9 Kristinsson A. Diagnosis, natural history, and treatment of congestive cardiomyopathy. University of London, 1969:188. PhD Thesis.

10 Grant C, Raphael MJ, Steiner RE, Goodwin JF. Left ventricular volume and hypertrophy in outflow obstruction. *Cardiovasc Res* 1968;4:346–55.

11 Parrillo JE, Aretz HT, Palacios I, Fallon JT, Block PC. The results of tranvenous endomyocardial biopsy can frequently be used to diagnose myocardial diseases in patients with idiopathic heart failure: endomyocardial biopsies in 100 consecutive patients revealed a substantial incidence of myocarditis. *Circulation* 1984;69:93–101.

12 Roberts WC, Ferrans VJ. Pathologic anatomy of the cardiomyopathies: idiopathic dilated and hypertrophic types, infiltrative types, and endomyocardial disease with and without eosinophilia. *Hum Pathol* 1975;6:287–342.

13 Olsen ECG. Pathology of primary cardiomyopathies. *Postgrad Med J* 1972;48:732–7.

14 Croxson R, Raphael MJ. Angiographic assessment of congestive cardiomyopathy [Abstract]. *Br Heart J* 1969;31:390.

15 Fitchett DH, Sugrue DD, MacArthur CG, Oakley CM. Right ventricular dilated cardiomyopathy. *Br Heart J* 1984;51:25–9.

16 Goodwin JF. Congestive and hypertrophic cardiomyopathies. A decade of study. *Lancet* 1970;i:731–9.

17 Hamby RI. Primary myocardial disease. A prospective clinical and haemodynamic evaluation in 100 consecutive patients. *Medicine (Baltimore)* 1970;49:55–78.

18 Hatle L, Orjavik O, Storstein O. Chronic myocardial disease I. Clinical picture related to long-term prognosis. *Acta Med Scand* 1976;199:399–405.

19 Shugoll GI, Bowen PJ, Moore JP, Lenkin ML. Follow-up observations and prognosis in primary myocardial disease. *Arch Intern Med* 1972;129:67–72.

20 Dye CL, Rosenbaun D, Lowe JC, Behnke RH, Genovese PD. Primary myocardial disease. Part I: clinical features. *Ann Intern Med* 1963;85:425–41.

21 Greenwood RD, Nadas AS, Fyler DC. The clinical course of primary myocardial disease in infants and children. *Am Heart J* 1976;92:549–60.

22 Huang SK, Messer JV, Denes P. Significance of ventricular tachycardia in idiopathic dilated cardiomyopathy: observations in 35 patients. *Am J Cardiol* 1983;51:507–12.

23 Von Olshausen K, Schäfer A, Mehmel HC, Schwarz F, Senges J, Kubler W. Ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Br Heart J* 1984;51:195–201.

24 Hatle L, Stake G, Storstein O. Chronic myocardial disease II. Haemodynamic findings related to long-term prognosis. *Acta Med Scand* 1976;199:407–11.

25 Goodwin JF. Treatment of the cardiomyopathies. *Am J Cardiol* 1973;32:341–51.

26 Franciosa JA. Effectiveness of long-term vasodilator administration in the treatment of chronic left ventricular failure. *Prog Cardiovasc Dis* 1982;24:319–30.

27 Franciosa JA. Long-term vasodilator therapy of chronic left ventricular failure: does it work? *Int J Cardiol* 1984;5:433–9.

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Case reports

Ebstein's anomaly of the tricuspid and mitral valves in an otherwise normal heart

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SUMMARY A case in which there was Ebstein's anomaly of both the tricuspid and mitral valve is described: the structure of the heart was otherwise normal.

The anomaly of the tricuspid valve first described by Ebstein in 1866[1 2] accounts for approximately 1% of all heart malformations.[3 4] It consists of the downward displacement of the basal insertion of the septal and posterior valve leaflets, which are almost always dysplastic.[5 6] In 42–97% of cases there is also an atrial septal defect or a patent foramen ovale and the anomaly may be associated with various other cardiac malformations.[7 8] Mital prolapse, contraction-relaxation abnormalities of the left ventricle, and mitral stenosis have also been reported,[3 9–11] In nearly half the affected hearts there is malformation of the left-sided atrioventricular valve in corrected transposition of the great arteries.[12] In the very rare cases in which there is malformation of the true mitral valve[6 13 14] the posterior leaflet is displaced downwards and there may be shortening of the outflow chamber.

We report a case of Ebstein's anomaly of both atrioventricular valves in an otherwise normal heart. This, to the best of our knowledge, has not been reported before.

Case report

The patient, a boy, was born at term on 6 May 1985 to a 31 year old woman (para 2, gravida 2) after an uneventful pregnancy (no history of drug administration or of infectious diseases). The Apgar scores at 1, 5, and 10 minutes were 6, 7, and 8 but the baby was cyanosed. Hypertelorism, retrognathia, widely spaced nipples, and stiffness of elbows and knees (with maximum extension to 130°) were noted. There was left cryptorchidism and slight epispadias. Tachypnoea (92/minute) was seen at birth; pulses were regular (130/minute) and symmetrical in all four extremities. A systolic/diastolic murmur was heard soon after birth but by two weeks of age it became a 4–5/6 pansystolic regurgitant murmur and a 3/6 diastolic tricuspid murmur; B1 was soft and B2 normally split. Chest x ray demonstrated cardiomegaly with a cardiothoracic index of 0·63. Electrocardiography showed right atrial and right ventricular hypertrophy, right bundle branch block, and right axis deviation (+ 180°) which became extreme (220°) over the following months.

Echocardiographic studies were performed at the age of two days, six days, and six months. These showed situs solitus as well as atrioventriculo-arterial concordance and connection. Both atria were significantly dilated and both atrioventricular valve insertions were abnormal: the anterior tricuspid leaflet was normally attached but the posterior and septal leaflets were displaced towards the apex. All three leaflets were dysplastic with thickened free edges. The anterior leaflet showed undulating, whip-like motions towards the right ventricular wall. Important tricuspid insufficiency was noted on Doppler echocardiographic examination. The mitral valve had a normally attached but thickened anterior leaflet; the insertion of the posterior leaflet was displaced towards the apex and the leaflet was dysplastic (fig 1a and b). All chordae were shortened. Doppler echocardiography also showed considerable mitral insufficiency. In addition, there was evidence of a ductus arteriosus at the first examination, which closed by six days.

Physiological pulmonary hypertension and resistance regressed during the first six days of life and the signs of right ventricular failure and cyanosis

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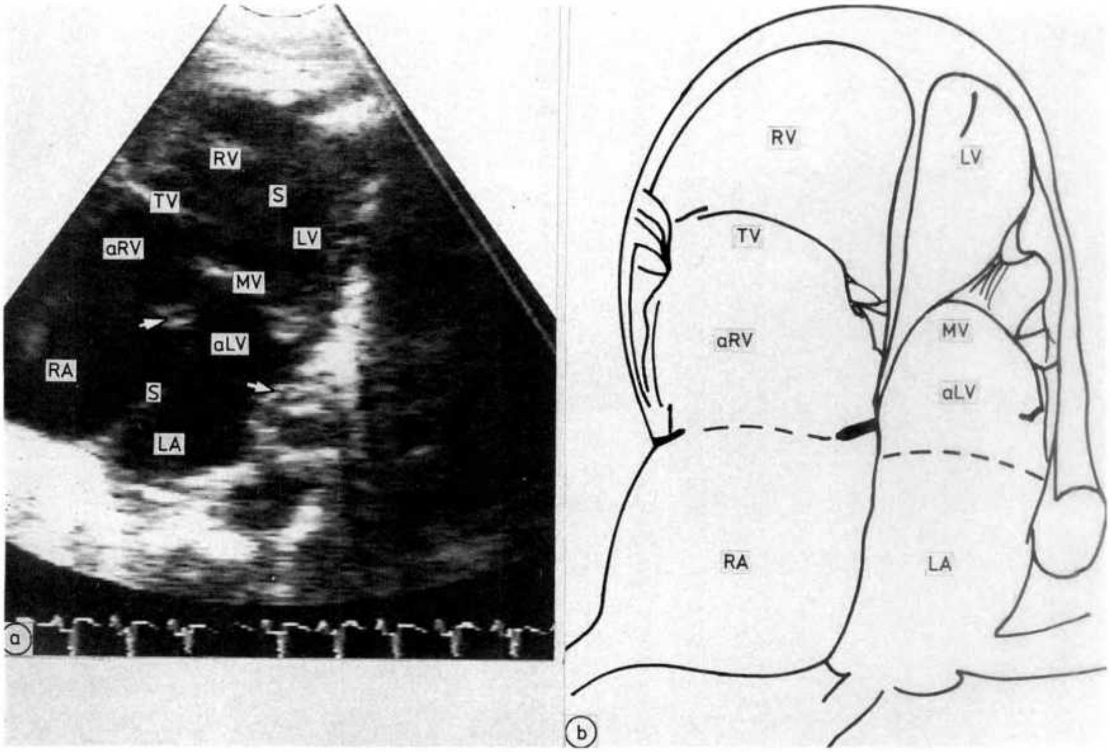

Fig 1 *Real time echocardiogram (a) and diagram (b) of the four chamber view of a case of Ebstein's anomaly of both atrioventricular valves. This shows apical displacement of the insertion of the septal and posterior leaflets of the tricuspid valve (TV) and of the insertion of the septal portion of the posterior leaflet of the mitral valve (MV). The atrialised portions of the right (aRV) and left (aLV) ventricles are well defined by the corresponding annulus fibrosis at the antrioventricular groove (arrowed). The moderator band is seen in the functional right ventricle (RV). The interventricular and interatrial septa (S) are intact. RA, right atrium, LA, left atrium, LV, left ventricle.*

became less conspicuous. Nevertheless, digoxin treatment was required.

Bilateral hydronephrosis caused by urethral strictures required drainage by cystostomy. After this renal function became normal. At the age of one month the patient was readmitted with a urinary infection. In October 1985 the proximal urethral mucosa was sutured to the skin to relieve urethral obstruction.

On 7 February 1986 the child was admitted with vomiting and diarrhoea, fever (39°–40° C), dehydration, and tachycardia (180/min) caused by viral gastroenteritis. There was no evidence of bacterial infection and the cerebrospinal fluid examination was unremarkable. Intravenous rehydration was necessary. At 4 pm on 8 February he had a sudden cardiorespiratory arrest and despite immediate and vigorous attempts at resuscitation he died one hour later.

PATHOLOGICAL EXAMINATION:

At necropsy the child was a well nourished boy weighing 7 kg (P 30) for a crown-heel length of 66 cm (P 30). Cranial circumference was 45·8 cm (P 50). There was straw-coloured fluid in the abdomen (25 ml) and in both pleural cavities (8 and 10 ml).
Heart.—The heart weighed 95 g (normal 42 g). The right atrium was dilated and hypertrophied (mean muscle thickness 2–3 mm). The structure of the interatrial septum was normal with a 3 mm diameter foramen ovale. The tricuspid valve was cone shaped, and its leaflets were thickened with rolled edges. It was difficult to identify individual leaflets (fig 2). The site of insertion of its anterior portion was normal while the insertions of the septal and posterior portions were displaced downwards. The chordae were short and thickened to such an extent that in some areas they were absent. The atrialised supravalvar right ventricle did not show noticeable thinning or

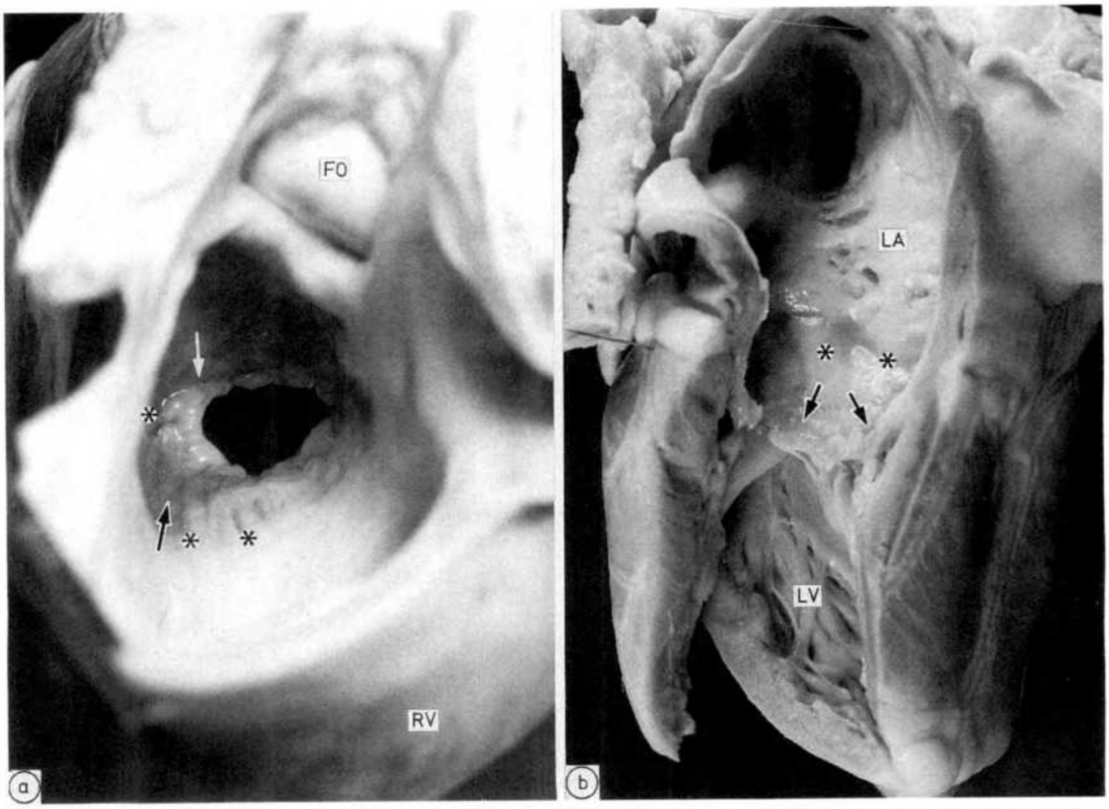

Fig 2 *(a) Tricuspid valve seen from right atrium in a case of Ebstein's anomaly. The basal insertion of posterior and septal portions is indicated (arrowed). Note narrow anterior leaflet. *annulus fibrosus; RV, right ventricle; FO, foramen ovale. (b) Left heart showing the downward displacement of the basal insertion of the septal part of the mitral valve which is dysplastic and inserted directly on to the medial papillary muscle (arrowed). There is dilatation and hypertrophy of left atrium. *position of normal insertion of mitral valve; LA, left atrium; LV, left ventricle.*

dilatation. The rest of the right ventricle was both dilated and markedly hypertrophied, but the configuration of the outflow tract and pulmonary valve was normal. The left atrium was dilated and hypertrophied (fig 2b). The mural portion of the posterior mitral valve leaflet was displaced downwards to the upper limit of the trabecular portion of the left ventricle (fig 2b). Both leaflets were dysplastic, and the chordae were significantly shortened and thickened or absent (fig 2b). The atrialised supravalvar ventricular wall was also thickened. The hypertrophic left ventricle and the aortic valve were otherwise normal. Histological examination showed several small foci of acute right myocardial necrosis that were attributed to cardiac massage.

The lungs showed signs of congestion and moderate interstitial and intra-alveolar oedema without evidence of infection. There was moderate right hydronephrosis caused by hypertrophic stenosis of the pyeloureteral junction and evidence of chronic pyelonephritis.

Discussion

In typical cases of Ebstein's anomaly the normally inserted anterior leaflet of the tricuspid valve may be a large and sail-like structure[4 15] whereas the septal and posterior valves are usually dysplastic and there is downward displacement of their basal insertion.[6 15] This arrangement permits the anterior valve to function as a monocusp valve after ventricular plication.[15] Furthermore, the right ventricle is divided into an atrialised supravalvar portion with quite thin walls and a trabecular, functional portion.[3 5 15] The size and degree of the dysfunction of the upper part of the ventricle as well as the degree of valvar insufficiency determine right ventricular function and right atrial pressure; when right atrial pressure exceeds left atrial pressure a right-left shunt through an interatrial communication or a patent foramen ovale causes cyanosis. In the present case the anterior leaflet of the tricuspid valve was not enlarged, and the dysplasia affected all leaflets roughly to the same degree, so that the insufficient tricuspid orifice was centrally sited. Regression of cyanosis during the first few days of life was mainly the result of closure of the ductus arteriosus. Because pressures in both atria were probably raised to a similar degree it is unlikely that there was important shunting through the patent foramen ovale.

The morphology of the mitral valve was similar to two previously reported cases of Ebstein's anomaly of the true mitral valve.[6 13] In the case described by Allenstein *et al*, however, there was a large ventricular septal defect and a hypoplastic left ventricle which contributed to the malformation of the mitral valve.[14] There was clinical and morphological evidence of mitral valve insufficiency in the case described by Ruschhaupt *et al.*[13] Recently, Leung *et al* have described two additional cases of this very rare anomaly.[16] In our case insufficiency of the dysplastic mitral valve was identified by Doppler echocardiography and hypertrophy and dilatation of the left atrium.

Ebstein's anomaly of the tricuspid valve can be confidently diagnosed by real time echocardiography.[17–19] The normally inserted mitral valve is used as the reference marker to indicate the correct position of the right valve insertion in the apical four chamber view. This is the most appropriate view to assess the annulus and the apical displacement of the insertion of the leaflets of the right atrioventricular valve and their motion. Additional views permit grading of displacement of the atrioventricular valve as well as a detailed evaluation of the severity and the specific form of any associated malformations.

In our case the diagnosis proved to be difficult because both atrioventricular valves were affected to a similar degree by the apical displacement of leaflet insertion and there was no mitral reference point for examination of the tricuspid valve. Furthermore, because both valves were severely dysplastic and did not close during systole there was bilateral atrioventricular valve insufficiency. The correlation between the echocardiographic and the pathological findings was good and retrospective analysis of the echocardiographic recordings in the light of the pathological findings confirmed the initial diagnosis.

Right bundle branch block was seen in our case. This is a frequent electrocardiographic abnormality in Ebstein's anomaly, as are modifications reflecting the atrial hypertrophy and the Wolff-Parkinson-White pattern of conduction.[8 20 21] These electrocardiographic findings are often the result of right bundle branch malpositions and of accessory atrioventricular connections[3 5 8] which predispose these patients to sudden, fatal arrhythmias.[22–25] We believe that such an arrhythmia is the most plausible cause of death in this case. The presence of an accessory atrioventricular connection and progressive, severe heart failure are the two major indications for surgical treatment of Ebstein's anomaly.[8 15] Neither was seen in the present case; furthermore replacement of both atrioventricular valves would have required anticoagulation and further valve replacement with growth and this treatment would not have prevented sudden, possibly fatal, arrhythmias.[15]

Despite an extensive review of published reports, we did not find another report of the association of Ebstein's anomaly of the tricuspid valve with the same malformation of the mitral valve.

References

1 Ebstein W. Ueber einen sehr seltenen Fall von Insufficienz der Valvular tricuspidalis, bedingt durch eine angeborene hochgradige Missbildung derselben. *Archiv für Anatomie, Physiologie und wissenschaftliche Medizin* 1866;238–54.

2 Schiebler GL, Gravenstein JS, Van Mierop LHS. Ebstein's anomaly of the tricuspid valve. Translation of original description with comments. *Am J Cardiol* 1968;**22**:867–73.

3 Lev M, Liberthson RR, Joseph RH, *et al.* The pathologic anatomy of Ebstein's disease. *Arch Pathol* 1970;**90**:334–43.

4 Anderson KR, Lie JT. Pathologic anatomy of Ebstein's anomaly of the heart revisited. *Am J Cardiol* 1978;**41**:739–45.

5 Anderson KR, Zuberbuhler JR, Anderson RH, Becker AE, Lie JT. Morphologic spectrum of Ebstein's anomaly of the heart. A review. *Mayo Clin Proc* 1979;**54**:174–80.

6 Becker AE, Anderson RH. Atrioventricular valve malformations. In: Becker AE, Anderson RH, eds. *Pathology of congenital heart disease*. London: Butterworths, 1981:137–63.

7 Watson H. Natural history of Ebstein's anomaly of tricuspid valve in childhood and adolescence. An international co-operative study of 505 cases. *Br Heart J* 1974;**36**:417–27.

8 Westaby S, Karp RB, Kirklin JW, Waldo AL, Blackstone EH. Surgical treatment in Ebstein's malformation. *Ann Thorac Surg* 1982;**34**:388–95.

9 Worms AM, Ravault MC, Ethevenot G, Hoeffel JC, Pernot C. Prolapsus mitral et anomalies ventriculaires gauches dans la malformation d'Ebstein de la tricuspide. A propos de 17 observations. *Arch Mal Coeur* 1980;**73**:499–508.

10 Roberts WC, Glancy DL, Seningen RP, Maron BJ, Epstein SE. Prolapse of the mitral valve (floppy

valve) associated with Ebstein's anomaly of the tricuspid valve. *Am J Cardiol* 1976;38:377–82.

11 Monibi AA, Neches WH, Lenox CC, Park SC, Mathews RA, Zuberbuhler JR. Left ventricular anomalies associated with Ebstein's malformation of the tricuspid valve. *Circulation* 1978;57:303–6.

12 Anderson KR, Danielson GK, McGoon DC, Lie JT. Ebstein's anomaly of the left-sided tricuspid valve. Pathological anatomy of the valvular malformation. *Cardiovasc Surg* 1978;58:I-87–91.

13 Ruschhaupt DG, Bharati S, Lev M. Mitral valve malformation of Ebstein type in absence of corrected transposition. *Am J Cardiol* 1976;38:109–12.

14 Allenstein BJ, Amromin GD, Henning AJ. An unusual cardiac anomaly: Ebstein-like malformation of the left atrioventricular valve, masquerading as a dextrocardia. Report of a case. *Dis Chest* 1963;44:642–8.

15 Danielson GK, Fuster V. Surgical repair of Ebstein's anomaly. *Ann Surg* 1982;196:499–504.

16 Leung M, Rigby ML, Anderson RH, Wyse RKH, Macartney FJ. Reversed offsetting of the septal attachments of the atrioventricular valves and Ebstein's malformation of the morphologically mitral valve. *Br Heart J* 1987;57:184–7.

17 Gussenhoven WJ, Spitaels SEC, Bom N, Becker AE. Echocardiographic criteria for Ebstein's anomaly of tricuspid valve. *Br Heart J* 1980;43:31–7.

18 Nihoyannopoulos P, McKenna WJ, Smith G, Foale R. Echocardiographic assessment of the right ventricle in Ebstein's anomaly: relation to clinical outcome. *J Am Coll Cardiol* 1986;8:627–35.

19 Shiina A, Seward JB, Edwards WD, Hagler DJ, Tajik AJ. Two-dimensional echocardiographic spectrum of Ebstein's anomaly: detailed anatomic assessment. *J Am Coll Cardiol* 1984;3:356–70.

20 Giuliani ER, Fuster V, Brandenburg RO, Mair DD. Ebstein's anomaly. The clinical features and natural history of Ebstein's anomaly of the tricuspid valve. *Mayo Clin Proc* 1979;54:163–73.

21 Kastor JA, Goldreyer BN, Josephson ME, *et al.* Electrophysiologic characteristics of Ebstein's anomaly of the tricuspid valve. *Circulation* 1975;52:987–95.

22 Radford DJ, Graff RF, Neilson GH Diagnosis and natural history of Ebstein's anomaly. *Br Heart J* 1985;54:517–22.

23 Kumar AE, Fyler DC, Miettinen OS, Nadas AS. Ebstein's anomaly. Clinical profile and natural history. *Am J Cardiol* 1971;28:84–95.

24 Oh JK, Holmes DR, Hayes DL, Porter CJ, Danielson GK. Cardiac arrhythmias in patients with surgical repair of Ebstein's anomaly. *J Am Coll Cardiol* 1985;6:1351–7

25 Rossi L, Thiene G. Mild Ebstein's anomaly associated with supraventricular tachycardia and sudden death: clinicomorphologic features in 3 patients. *Am J Cardiol* 1984;53:332–4.

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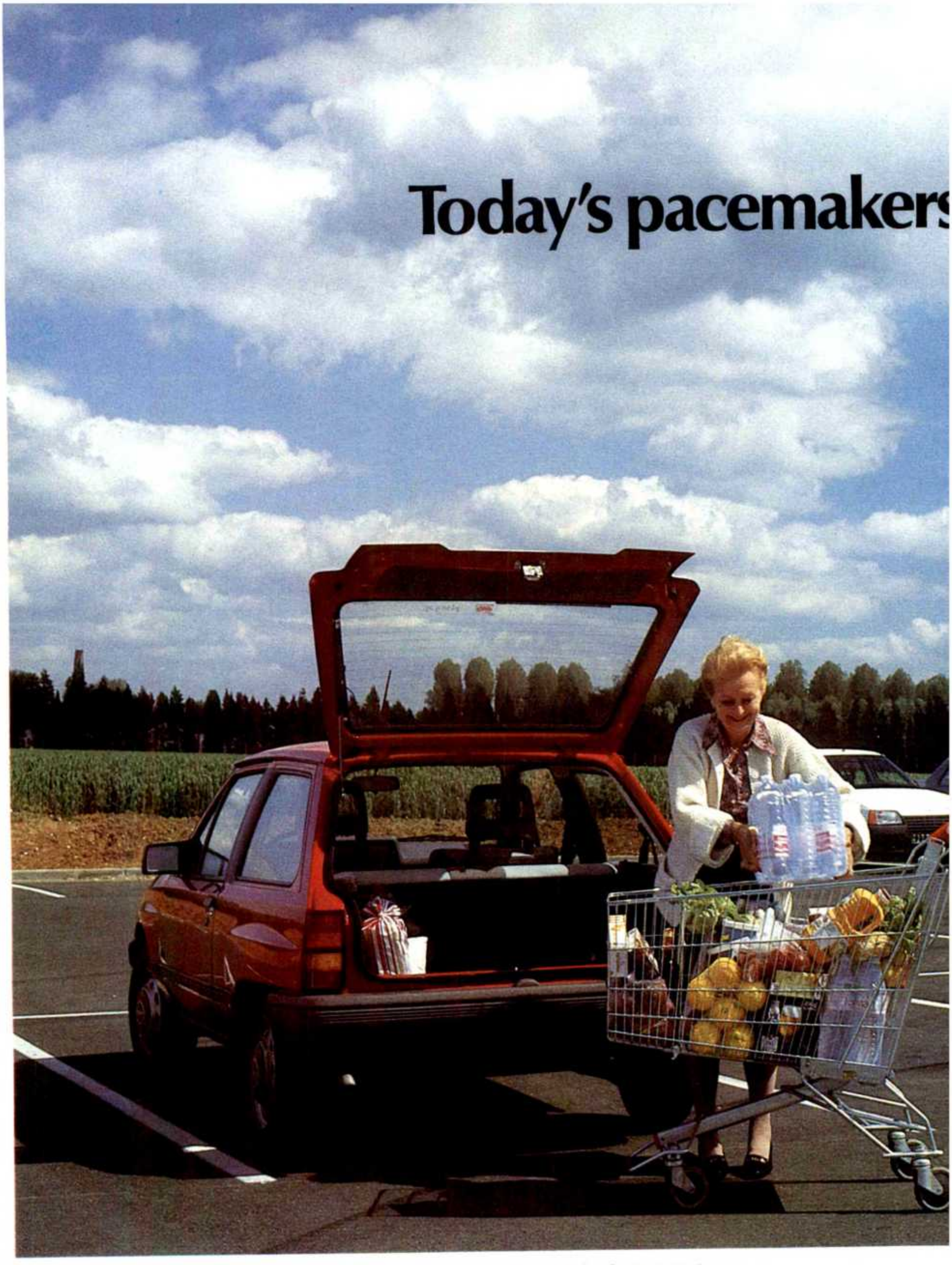

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"Late" manifestations of cardiovascular syphilis occurring in a young man

A P BROWN, K D DAWKINS, D J PARKER

From the Regional Cardiothoracic Unit, St George's Hospital, London

SUMMARY A young man who presented with a short history of angina was found to have syphilitic coronary ostial stenosis six years after the primary infection. He was successfully treated with bilateral internal mammary grafts.

Syphilis became a rare disease in the West after the widespread use of penicillin in the 1950s. The present incidence in the United Kingdom has fallen to less than 4000 new cases per annum.[1] The late manifestations of the disease are now so rare that they are generally considered to be medical curiosities, although occasional cases are seen in elderly patients who contracted the infection before penicillin became generally available.

Case report

A 25 year old farmer presented with a three week history of chest pain typical of angina occurring on moderate exertion. He had previously been very fit and active. He smoked 10 cigarettes daily and occasional cannabis. He gave no history of genital ulceration or venereal infection and he denied any homosexual relationships. The most likely source of infection was thought to have been a casual contact six years previously while he was on holiday in India. There was a positive family history of ischaemic heart disease: his father had undergone coronary artery bypass grafting at the age of 54 years and his grandfather had sustained a myocardial infarct in his 50s.

On examination there were no features of congenital syphilis or stigmata of hyperlipidaemia. Blood pressure was 110/60 mm Hg, and heart sounds were normal with no murmurs. Detailed neurological examination showed no abnormality. Full blood count, urea, electrolytes, liver function tests, and a fasting lipid profile were all normal. The erythrocyte sedimentation rate was 10 mm in one hour. A rapid plasma reagin card test for syphilis was positive at a low titre of 1:8 and the *Treponema pallidum* haemagglutinating antibody and FTA(ABS) tests were also positive. The cerebrospinal fluid contained 0·4 gs/litre of protein and serology was negative.

The resting electrocardiogram and chest radiograph were normal. During a formal treadmill exercise test the haemodynamic response was normal but the patient developed chest pain during stage five of the standard Bruce protocol. The pain was associated with 4 mm horizontal ST segment depression.

At cardiac catheterisation the pressures were all normal. Aortography showed minor irregularity of a normal sized aortic root. There was no aortic regurgitation. A tight left coronary ostial stenosis (fig 1a) prevented engagement of an 8F catheter, and a moderate stenosis of the right coronary ostium just allowed entry of the catheter. Introduction of the catheter into either ostium resulted in an immediate fall in pressure with "ventricularisation" of the pressure trace. Aortic sinus injections confirmed the presence of bilateral ostial stenosis and the administration of nitrates did not alter the appearances. The distal coronary vessels were normal.

At operation the ascending aorta was found to be thickened and inflamed. There was a sharp line of demarcation with apparently normal aorta 1 cm above the supra-aortic ridge. The aortic valve cusps were entirely normal. Neither coronary ostium permitted the introduction of a 1 mm probe. The right internal mammary artery was grafted to the distal right coronary artery, the left internal mammary artery to the left anterior descending artery, and a saphenous vein graft to the left circumflex artery.

A biopsy specimen of the aortic wall showed severe aortitis with focal destruction of the media and fragmentation of the internal elastic laminae.

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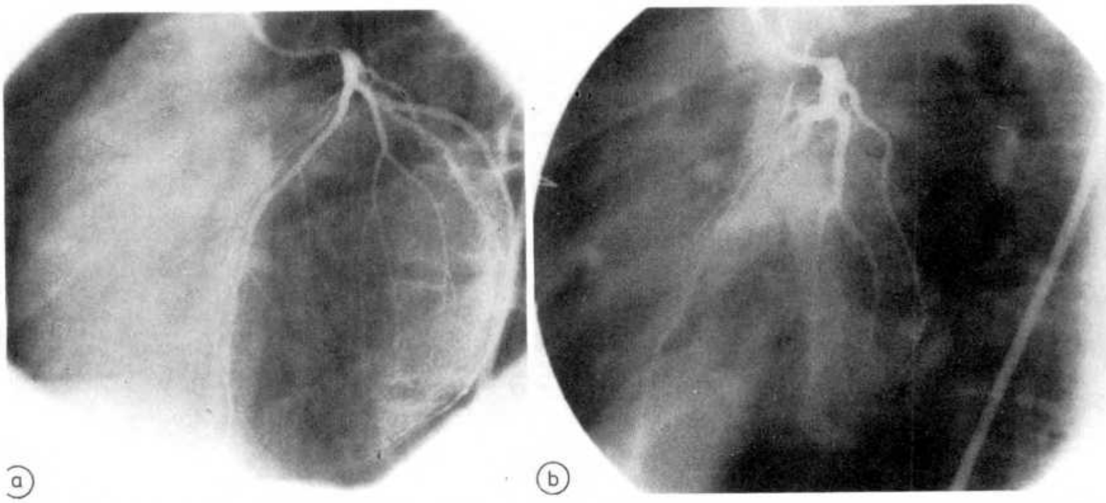

Fig 1 *Coronary arteriograms (a) showing left coronary ostial stenosis (left anterior oblique view) and (b) four months after operation showing enlargement of the left coronary ostium.*

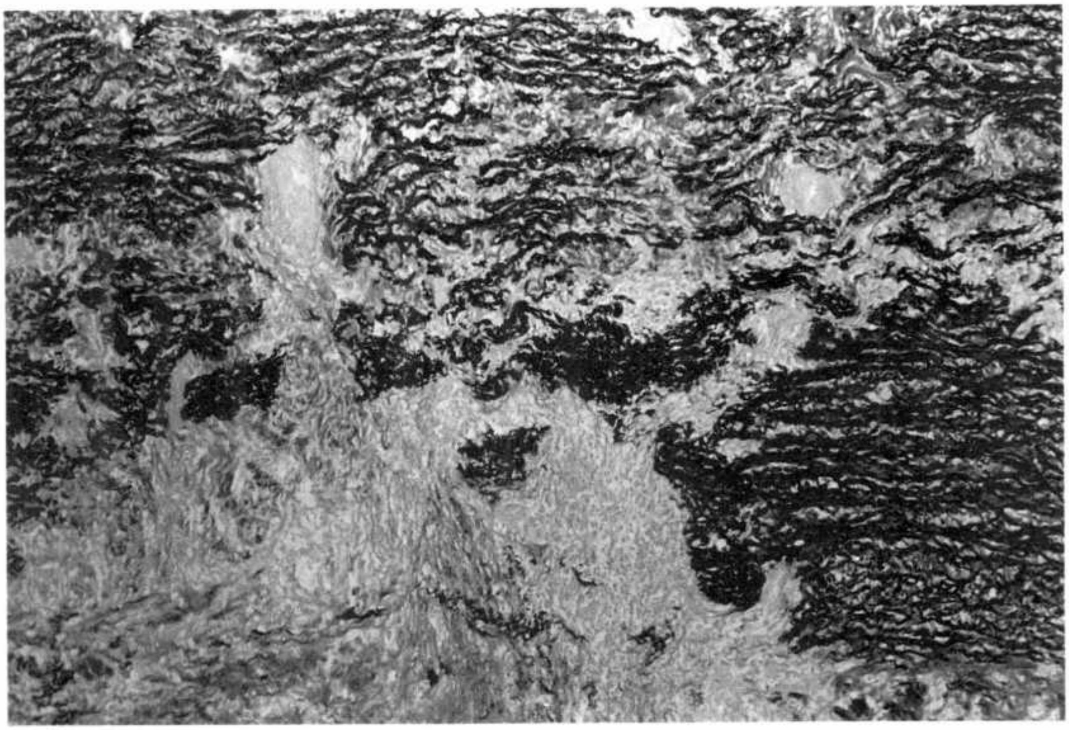

Fig 2 *Photomicrograph of biopsy specimen of the ascending aorta showing vasculitis, focal destruction of the media, and fragmentation of the elastic lamina associated with a florid inflammatory cell response. (Elastic-van Gieson, original magnification × 100.)*

There was a florid chronic inflammatory infiltrate with plasma cells around the vasa vasorum and within the adventitia (fig 2).

Postoperative recovery was uneventful. The patient was treated with prednisolone 10 mg twice daily for five days and procaine penicillin 1·8 mU intramuscularly daily for 21 days.

Subsequently he resumed normal activities and a follow up exercise test was normal. He underwent elective repeat catheterisation four months after operation. Aortography was normal. Both coronary ostia permitted engagement of an 8F catheter with ease (fig 1b) and all three coronary grafts were patent.

Discussion

Syphilis affects the cardiovascular system in several ways.[2] An aortitis is seen most frequently; this can lead to root dilatation, aneurysm formation, aortic regurgitation, and stenosis of the coronary ostia. Pathologically there is an endarteritis of the vasa vasorum associated with a mesoaortitis, patchy loss of elastic tissue, and fibrous replacement. Exceptionally rare manifestations of cardiovascular syphilis include myocardial gumma and coronary arteritis. Cardiac involvement is more common in men,[3] and there is also a reported association with systemic hypertension.[4]

Isolated coronary ostial stenosis is seen most frequently in association with atheromatous disease. It is found in approximately 0·1% of all patients investigated with coronary artery disease.[5] Necropsy data suggest that coronary ostial stenosis occurs in 20–30% of cases of cardiovascular syphilis.[6 7] Scharfman and colleagues noted a low incidence of myocardial infarction and suggested that this was due to the slow progression of the disease.[6] In contrast, Heggtveit reported a series of 100 cases of syphilitic aortitis[7]; 26 of these cases had coronary ostial stenosis, which was associated with aortic regurgitation in 14. There were 24 cases of myocardial infarction; four were caused by ostial stenosis and three by a combination of ostial stenosis and atheroma. Syphilis was thought to have been the primary cause of death in 33 cases, and sudden death occurred in five patients with coronary ostial stenosis.

Surgical treatment is aimed at increasing myocardial perfusion, either by some form of reconstructive procedure on the coronary ostium,[8–10] or alternatively by coronary artery bypass grafting. Dubost *et al* introduced endarterectomy for syphilitic coronary ostial stenosis in 1959.[8] The procedure was technically difficult, especially if the ostium was not visible from the aorta, and a considerable proportion of patients developed restenosis during long term follow up.[11] More recently, saphenous vein bypass grafts have been used in several centres,[12–15] but the superior long term patency of the internal mammary artery[16] may make this the conduit of choice.

We treated our patient with prednisolone as well as penicillin in an attempt to avoid the Jarisch-Herxheimer reaction. Sudden death is said to occur in this syndrome, possibly due to acute swelling of the aortic wall and occlusion of the coronary ostia. For this reason, antibiotic treatment was delayed until myocardial revascularisation had been undertaken.

The overall incidence of syphilis is falling slowly in the United Kingdom, and the proportion of patients presenting with late manifestations of the disease (currently one third) is rising.[1] In recent years most of these cases have been in patients in middle and old age. For example, in a series from Denmark between 1960 and 1970 105 patients presented with late syphilis of whom 92 were over the age of 45 years.[17] Forty patients had cardiovascular syphilis and six also had neurological involvement.

There will now be very few patients who contracted the disease before the antibiotic era, and so we should expect to see a higher proportion of younger patients in whom the early infection was not treated. Possible reasons for missing early syphilis include an asymptomatic infection, infection masked by antibiotics given for another reason (for example, gonorrhoea), and a low index of suspicion now that the disease is uncommon.

The latent period between exposure and late disease may be as short as three to five years and presentation in patients in their 20s is not unknown.[14] Syphilis has protean manifestations and mimicks many other diseases; it should not be forgotten as a cause of angina especially in a young patient.

We thank Dr E A F Davidson, Department of Genitourinary medicine for helpful advice.

References

1 Extract from the Annual Report of the Chief Medical Officer (1982). *Br J Vener Dis* 1984;60:199–203.

2 Silver MD. *Cardiovascular pathology*. Vol 2. New York: Churchill Livingstone 1983:707–37.

3 Clark EG, Danbolt M. The Oslo study of the natural course of untreated syphilis: an epidemiologic investigation based on a restudy of the Boeck-Bruusgaard material. *Med Clin N Am* 1964; 48:613–23.

4 Rockwell DH, Yobs AR, Moore MB. The Tuskegee

study of untreated syphilis: the thirtieth year of observation. *Arch Intern Med* 1964;**114**:792–8.

5 Hutter JA, Pasaoglu I, Williams BT. The incidence and management of coronary ostial stenosis. *J Cardiovasc Surg (Torino)* 1985;**26**:581–4.

6 Scharfman WB, Wallach JB, Angrist A. Myocardial infarction due to syphilitic coronary ostial stenosis. *Am Heart J* 1950;**40**:603–13.

7 Heggtveit HA. Syphilitic aortitis: a clinicopathologic autopsy study of 100 cases, 1950 to 1960. *Circulation* 1964;**29**:346–55.

8 Dubost C, Blondeau P, Piwnica A, *et al.* Syphilitic coronary obstruction: correction under artificial heart-lung and profound hypothermia at 10°C. *Surgery* 1960;**48**:540–7.

9 Connolly JE, Eldridge FL, Calvin JW, Stemmer EA. Proximal coronary artery obstruction: its aetiology and treatment by transaortic endarterectomy. *N Engl J Med* 1964;**271**:213–9.

10 Beck W, Barnard CN, Schrire V. Syphilitic obstruction of coronary ostia successfully treated by endarterectomy. *Br Heart J* 1965;**27**:911–5.

11 D'Allaines C, Lacour-Gayet F, Blondeau P, *et al.* Resultats a distance des coronarites ostiales operees. *Arch Mal Coeur* 1979;**72**:1173–9.

12 Michaud P, Chassignolle J, Age C, Champsaur G. Coronarite ostiale syphilitique: a propos de onze cas traites chirurgicalement. *Ann Chir* 1980;**34**:210–5.

13 Hirano M, Hawasuji M, Tsuchiya K, Watanabe Y, Fukatani G, Iwa G. Surgical treatment of syphilitic aortic insufficiency associated with stenosis of both coronary ostia. *Kyobu Geka* 1980;**33**:794–7.

14 Moraes CR, Oliveira PS, Rodrigues JV, Escobar M. Revascularizacao miocardica na estenose sifilitica da arteria coronaria esquerdo: relato de caso. *Arq Bras Cardiol* 1984;**42**:285–7.

15 Przybojewski JZ, Van Rensburg CJ. Syphilitic coronary ostial stenosis. *S Afr Med J* 1983;**64**:407–12.

16 Loop FD, Lytle BW, Cosgrove DM, *et al.* Influence of the internal-mammary-artery graft on 10 year survival and other cardiac events. *N Engl J Med* 1986;**314**:1–6.

17 Fischer A, Kristensen K, Husfelt V. Tertiary syphilis in Denmark 1961–1970: a description of 105 cases not previously diagnosed or specifically treated. *Acta Derm* 1976;**56**:485–8.

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Atrioventricular canal mimicking tricuspid atresia: echocardiographic and angiographic features

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SUMMARY In a rare case of common atrioventricular canal mimicking tricuspid atresia the clinical, radiographic, electrocardiographic, and M mode echocardiographic features were indistinguishable from those of classic tricuspid atresia. The cross sectional echocardiographic appearance and right atrial cineangiographic features were distinctive, however, and can be used to discriminate between this anomaly and other types of tricuspid atresia.

Case report

An eight year old boy was referred with a history of cyanosis since birth and decreased exercise tolerance in the past year. Height and weight were both below the fifth percentile. Physical examination showed cyanosis, clubbing, increased left ventricular impulse, prominent thrill at the left upper sternal border, single second heart sound, a grade 3/6 pansystolic murmur at the left lower sternal border, and a grade 4/6 long systolic murmur at the left upper sternal border.

A chest radiograph showed moderate cardiomegaly, decreased pulmonary vascular markings, and a left aortic arch. The electrocardiogram showed left axis deviation, evidence of left ventricular hypertrophy, and decreased anterior and rightward forces. An M mode echocardiogram showed a large left atrium, markedly enlarged left ventricle with normal left ventricular function, small right ventricle, and a large posterior atrioventricular valve that was continuous with a posterior semilunar valve presumed to be the aortic valve. No echoes were recorded for tricuspid or pulmonary valves. These findings were consistent with classic tricuspid atresia.[1 2] A cross sectional echocardiogram showed an ostium primum atrial septal defect, what seemed to be a common atrioventricular valve, and a small right ventricle (fig 1a and b). The entrance to the right ventricle seemed to be sealed off by a leaflet of the common atrioventricular valve.

The results of cardiac catheterisation (table) were consistent with classic tricuspid atresia. Selective left ventricular angiography revealed a large, well contracting left ventricle with prompt opacification of the right ventricle via a ventricular septal defect of moderate size. There was valvar and subvalvar pulmonary stenosis. Abnormal attachment of the mitral valve leaflets produced a "goose neck" deformity of the left ventricular outflow tract; this was partially obscured by the opacified right ventricle (fig 2a). A right atrial cineangiogram showed direct emptying of the contrast material into the left ventricle via the primum atrial septal defect and common atrioventricular valve (fig 2b). The left atrium was simultaneously opacified, unlike classic tricuspid atresia in which there is sequential opacification of the right atrium, left atrium, and left ventricle. The right ventricle was not directly opacified from the right atrium. The child underwent a right Blalock-Taussig shunt which improved systemic arterial oxygen saturation (84%).

Discussion

In this case the right sided component of a common atrioventricular valve occluded the entry of the right atrium into the right ventricle causing left ventricular dominance and underdevelopment of the right ventricle. This anomaly appears to be anatomically distinct from classic forms of tricuspid atresia but produces similar physiological effects. Most cases of tricuspid atresia are of the muscular type (89%).[3] Membranous, valvar, and Ebstein's type atresia each cause 3–4% of cases of tricuspid atresia.[3] Common atrioventricular canal mimicking tricuspid atresia is

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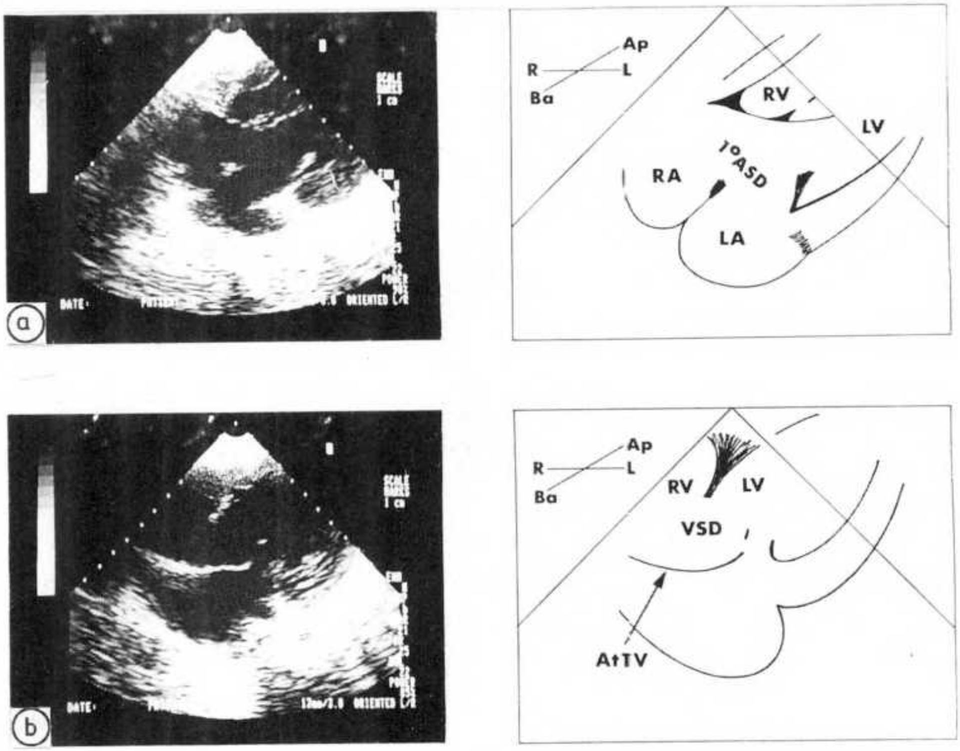


Fig 1 *Subcostal four chamber cross sectional echocardiographic views of the heart with an open (a) and almost closed (b) atrioventricular valve. Note the large ostium primum atrial septal defect (a). While it is open the large atrioventricular valve (a) permits emptying of both atria into the left ventricle (LV). The anterior leaflet of the atrioventricular valve occludes the right ventricle (RV) (from the right atrium (RA)) and ventricular septal defect (VSD). When it is closed (b) the atrioventricular valve continues to occlude the RV (At TV) while the VSD allows free communication between the ventricles. Ap, Apex; Ba, base; L, left; LA, left atrium; R, right.*

rarely reported and was only briefly mentioned by Van Praagh.[4] Such cases were not reported in Van Praagh *et al*'s initial series[5] or by Anderson *et al*, Weinberg, Bharati *et al*, Quero Jimenez, and Ando *et al*.[6–10]

Table *Cardiac catheterisation data*

Site	*Oxygen saturation (%)*	*Pressure (mm Hg)*
Superior vena cava	29	—
Inferior vena cava	32	—
Right atrium	32	a–10, V–8, mean–4·5
Pulmonary vein	95	—
Left atrium	78	a–8, V–8, mean–4
Left ventricle	75	110/6
Aorta	71	110/65, mean 86
Qp:Qs	1·6	

The clinical, radiographic, and electrocardiographic features of this case were indistinguishable from those of tricuspid atresia as were the findings on the M mode echocardiogram. The characteristic abnormal, superiorly oriented major QRS vector (left axis deviation) in the frontal plane seen with common atrioventricular canal is a distinguishing feature; however, patients with tricuspid atresia also have similar orientation of the QRS vector,[11] but for different electrophysiological reasons.[12 13]

The cross sectional echocardiographic features of tricuspid atresia have been well described.[14 15] In the most common muscular type, a dense band of echoes is seen at the site where the tricuspid valve should be[1 14] whereas in the membranous type the atrial floor is much thinner and moves back and forth into the atrial and ventricular cavity during systole and diastole.[15 16] In both types the anterior leaflet of the detectable atrioventricular valve is

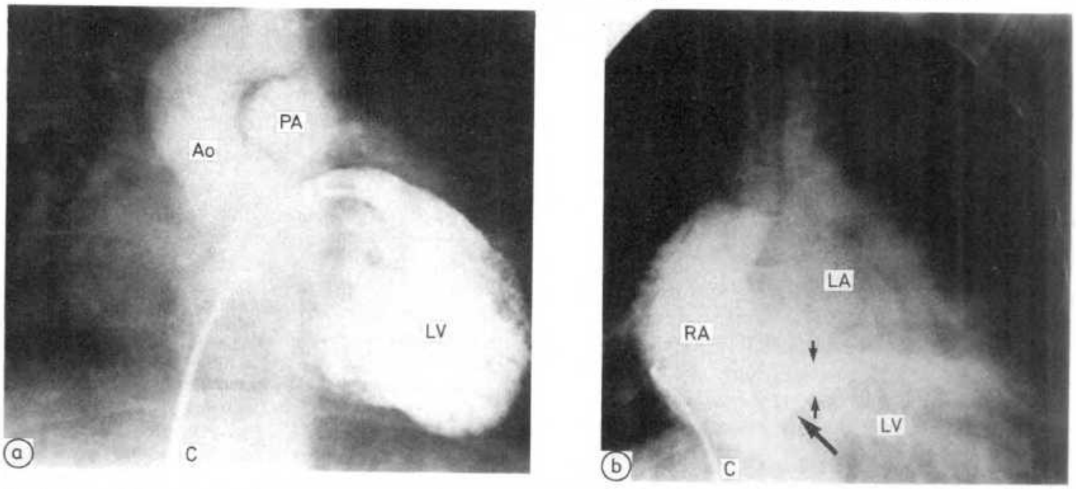
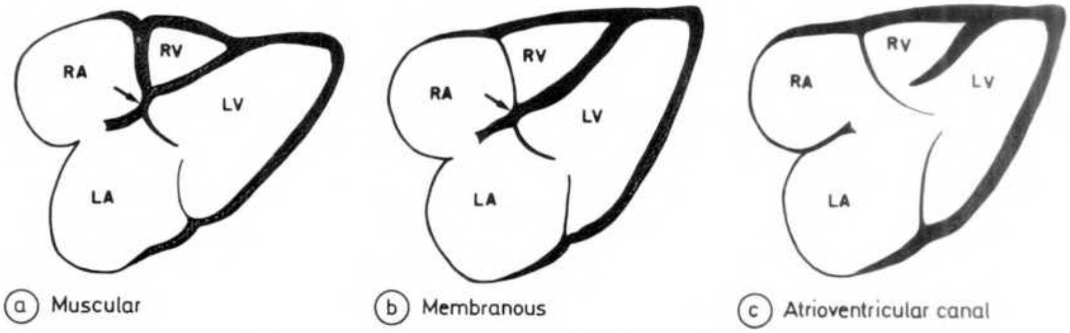


Fig 2 *(a) Selected frame from the left ventricular (LV) cineangiogram in the posteroanterior view. A large left ventricle is seen with opacification of aorta (Ao) and main pulmonary artery (PA); the latter is opacified through the right ventricle. Note the abnormal left ventricular outflow tract which is similar to the "goose-neck" deformity seen in endocardial cushion defects and is presumably related to abnormal attachment of the anterior leaflet of the mitral valve. (b) Right atrial (RA) cineangiographic frame in posteroanterior view. The floor of the right atrium is formed by a leaflet of the atrioventricular valve (large arrow). Note exit of the contrast material via an ostium primum atrial septal defect (small arrows) with opacification of the left ventricle (LV). The left atrium (LA) is only faintly opacified. There was no opacification of the right ventricle. C, catheter.*

attached to the left side of the interatrial septum[14] and the echocardiographic crux cordis (produced by the spatial arrangement of the atrial and ventricular septal planes and the plane of the atrioventricular junction) can be demonstrated.[15 16] In this case the appearance of crux cordis on the cross sectional echocardiogram was abnormal. A large atrioventricular leaflet from the right side occluded the



(a) Muscular (b) Membranous (c) Atrioventricular canal

Fig 3 *A drawing showing the cross sectional echocardiographic appearance (subcostal four chamber views) of the muscular, membranous, and atrioventricular canal types of tricuspid atresia. In the muscular type, the atretic tricuspid valve is represented by a thick band of echoes guarding the small right ventricle (RV) while in the membranous type the tricuspid valve is represented by a thin line. In both these the crux of the heart is well visualised. Note the attachment of the anterior leaflet of the detectable atrioventricular valve to the left side of the interatrial septum. The drawing also shows the atrioventricular portion of the interventricular septum (arrows) inferior to (toward left ventricular apex) the attachment of this valve leaflet. In tricuspid atresia of the atrioventricular canal type, the anterior leaflet of the detectable atrioventricular canal is attached to the anterior wall of the heart; it occludes the right ventricle from the right atrium and permits exit of both atria into the left ventricle. An ostium primum atrial septal defect is also shown. Major components of the crux cordis, including the atrioventricular portion of the interventricular septum, are missing.*

right ventricle and the ventricular septal defect when the atrioventricular valve was open (fig 1a). When the atrioventricular valve (fig 1b) was closed the right ventricle continued to be occluded and could not communicate with the right atrium. The ventricular septal defect provided a communication between the ventricles. Figure 3 shows the echocardiographic appearance of these three types of tricuspid atresia.

Right atrial angiography showed that the floor of the right atrium (large arrow, fig 2b) was formed by the atrioventricular valve leaflet and that the right atrium communicated with the left ventricle via an ostrium primum atrial septal defect (two small arrows, fig 2b). This was responsible for the simultaneous opacification of the left atrium and left ventricle during right atrial angiography. In classic tricuspid atresia there is sequential opacification of the left atrium and left ventricle.

The cross sectional echocardiographic and angiographic features of common atrioventricular canal mimicking tricuspid atresia distinguish this anomaly from classic tricuspid atresia.

References

1 Covitz W, Rao PS. Non-invasive evaluation of patients with tricuspid atresia (roentgenography, echocardiography and nuclear angiography). In: Rao PS, ed. *Tricuspid atresia.* Mt Kisco, New York: Futura, 1982:127–45.

2 Seward JB, Tajik AJ, Hagler DJ, Ritter DG. Echocardiographic spectrum of tricuspid atresia. *Mayo Clin Proc* 1978;**53**:100–12.

3 Rao PS. Classification of tricuspid atresia. In: Rao PS, ed. *Tricuspid atresia.* Mt Kisco, New York: Futura, 1982:41–7.

4 Van Praagh R. Discussion after paper by Vlad P. Pulmonary atresia with intact ventricular septum. In: Barrett-Boyes BG, Neutze JM, Harris EA, eds. *Heart disease in infancy: diagnosis and surgical treatment.* London: Churchill Livingstone, 1973:246–9.

5 Van Praagh R, Ando M, Dungan T. Anatomic types of tricuspid atresia: clinical and developmental implications [Abstract]. *Circulation* 1971;**44**(suppl II):115.

6 Anderson RH, Wilkinson JL, Gerlis LM, Smith A, Becker AE. Atresia of the right atrioventricular orifice. *Br Heart J* 1977;**39**:414–28.

7 Weinberg PM. Anatomy of tricuspid atresia and its relevance to current forms of surgical therapy. *Ann Thorac Surg* 1980;**29**:306–11.

8 Bharati S, McAllister HA, Tatooles CJ, *et al.* Anatomic variations in underdeveloped right ventricle related to tricuspid atresia and stenosis. *J Thorac Cardiovasc Surg* 1976;**72**:383–400.

9 Quero Jimenez M. Tricuspid atresia: an anatomical study of 17 cases. *Eur J Cardiol* 1975;**314**:337–48.

10 Ando M, Satomi G, Takao A. Atresia of tricuspid or mitral orifice: anatomic spectrum and morphogenetic hypothesis. In: Van Praagh R, Takao A, eds. *Etiology and morphogenesis of congenital heart disease.* Mt Kisco, New York: Futura, 1980:421–87.

11 Kulangara RJ, Boineau JP, Moore HV, Rao PS. Electrovectorcardiographic features of tricuspid atresia. In: Rao PS, ed. *Tricuspid atresia.* Mt Kisco, New York: Futura, 1982:113–26.

12 Durrer D, Roos JP, Van Dam R Th. The genesis of the electrocardiogram of patients with ostium primum defects (ventral atrial septal defects). *Am Heart J* 1966;**71**:642–50.

13 Boineau JP, Moore NE, Patterson DF. Relationship between the ECG ventricular activation and the ventricular conduction system in ostium primum ASD. *Circulation* 1973;**48**:556–64.

14 Beppu S, Nimura Y, Tamai M, *et al.* Two-dimensional echocardiography in diagnosing tricuspid atresia. Differentiation from other hypoplastic right heart syndromes and common atrioventricular canal. *Br Heart J* 1978;**40**:1174–83.

15 Rigby ML, Gibson DG, Joseph MC, *et al.* Recognition of imperforate atrioventricular valves by two dimensional echocardiography. *Br Heart J* 1982;**47**:329–36.

16 Magharini A, Azzolina G, Careri J. Anatomy of the echocardiographic crux cordis in the evaluation of the spectrum of atrioventricular valve atresia. *Int J Cardiol* 1984;**5**:163–72.

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Rapid growth of a left atrial myxoma shown by echocardiography

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SUMMARY Rapid growth of a left atrial myxoma was demonstrated in a patient who showed no echocardiographic evidence of the tumour when he was admitted for coronary artery bypass grafting. Eight months later he complained of dyspnoea and fatigue, and cross sectional echocardiography showed a 6 × 4 cm left atrial myxoma. This was removed and the diagnosis was confirmed by histological examination.

Although atrial myxomas are rare they are the most common primary cardiac tumour. With the development of cross sectional echocardiography the diagnosis of atrial myxoma at an earlier stage has become easier, and recognised cases are becoming more common. However, few data have been collected about the growth of the tumour. The interval from the onset of symptoms to operation or death varied from two days to eight years (mean 16 months) in the retrospective study of St John Sutton *et al.*[1] In the same study there were two recurrences within three years of resection.

We report the clinical, echocardiographic, angiographic, and morphological results in a patient in whom rapid growth of a left atrial myxoma over seven months was demonstrated.

Case report

A 45 year old man was referred to the Hôpital Cardiologique, Bordeaux, in April 1983 for evaluation of coronary artery disease a few weeks after an inferior myocardial infarction. At this first examination no murmur was heard. A cross sectional echocardiogram showed a normal sized left ventricle with reduced motion of the inferior wall. Mitral valve motion was normal and the left atrium was free of any visible mass (figs 1 and 2). A coronary angiogram showed three vessel disease with complete obstruction of the right coronary artery. Right ventriculography was not performed; there was no neovascularity of the atrium. The patient subsequently underwent coronary artery bypass surgery. The operation was successful and uncomplicated. A postoperative echocardiogram was normal except for showing evidence of persistent hypokinesia of the inferior wall. Eight months later the patient complained of fatigue and dyspnoea (class III New York Heart Association). Cardiac examination showed a regular rhythm, an accentuated first heart sound, and a diastolic sound. The appearance of the electrocardiogram was unchanged. A cross sectional echocardiogram showed a large globular mass (6 × 4 cm) in the left atrium, protruding through the mitral valve during diastole. The tumour was attached to the interatrial septum by a short broad stalk (figs 1 and 2). A pulmonary cineangiogram confirmed the presence of a large left atrial mass which moved through the mitral valve into the left ventricle during diastole. This filling defect was also visible during left ventriculography at the level of the inflow tract. It had not been present on the first left ventriculogram in April. Furthermore, selective angiography of the right coronary artery graft produced a tumour blush through small branches of the distal right coronary artery. A 5·5 × 4 cm tumour was removed. It had a smooth external surface and was attached to the interatrial septum. The mass had the typical gross and histological features of a myxoma. Light microscopy of haematoxylin and eosin stained sections disclosed typical scale-like myxoma cells. Alcian blue stained sections showed the extensive glycosaminoglycan ground substance that is characteristic of a myxoma matrix. A myxosarcoma was excluded. The patient remains well three years after operation.

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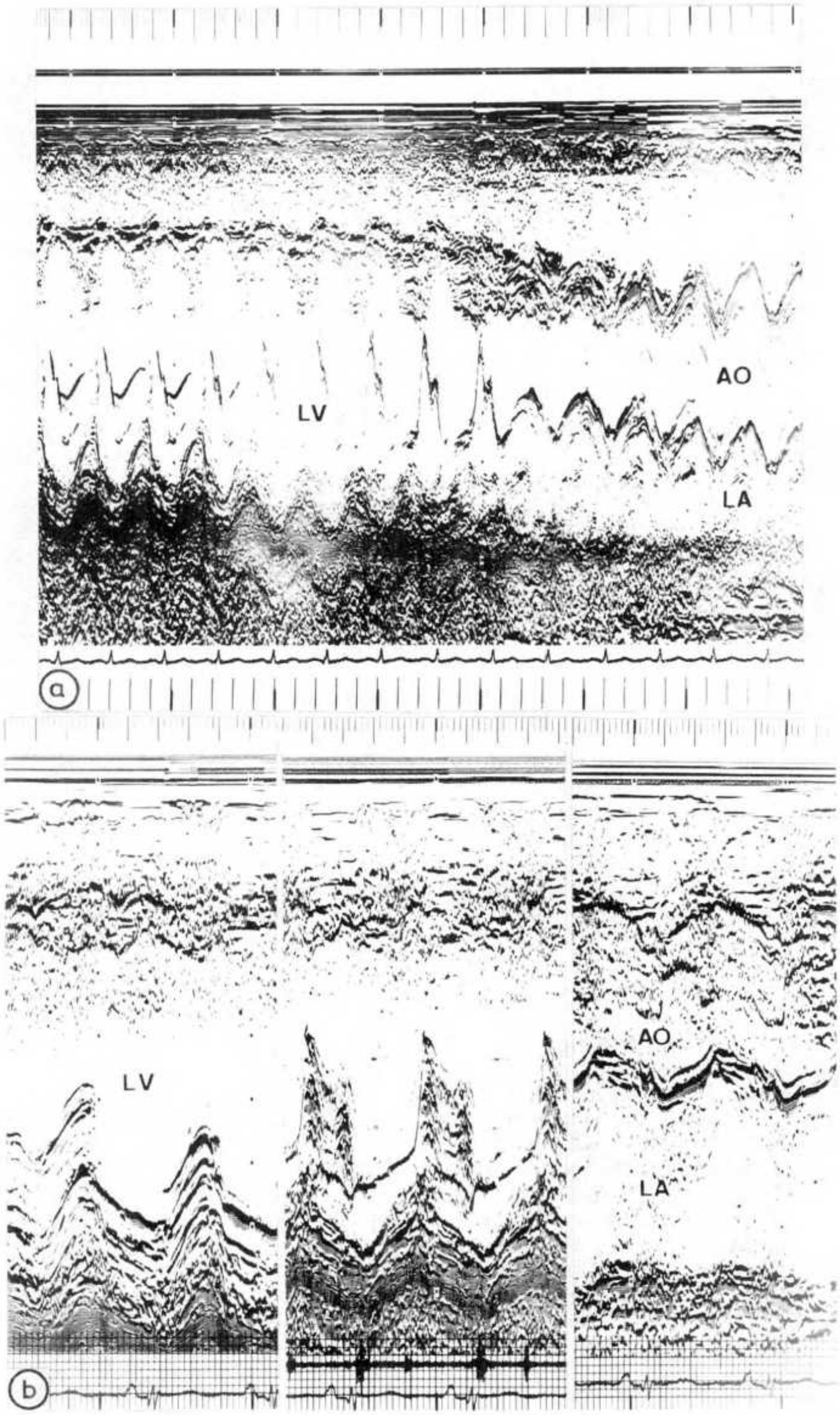

Fig 1 *M mode echocardiograms. (a) Recorded in April when mitral valve motion was normal and left atrium (LA) appeared to be free of any visible mass (LV, left ventricle). (b) Eight months later abnormal echoes showed the presence of a mass protruding through the mitral valve during diastole.*

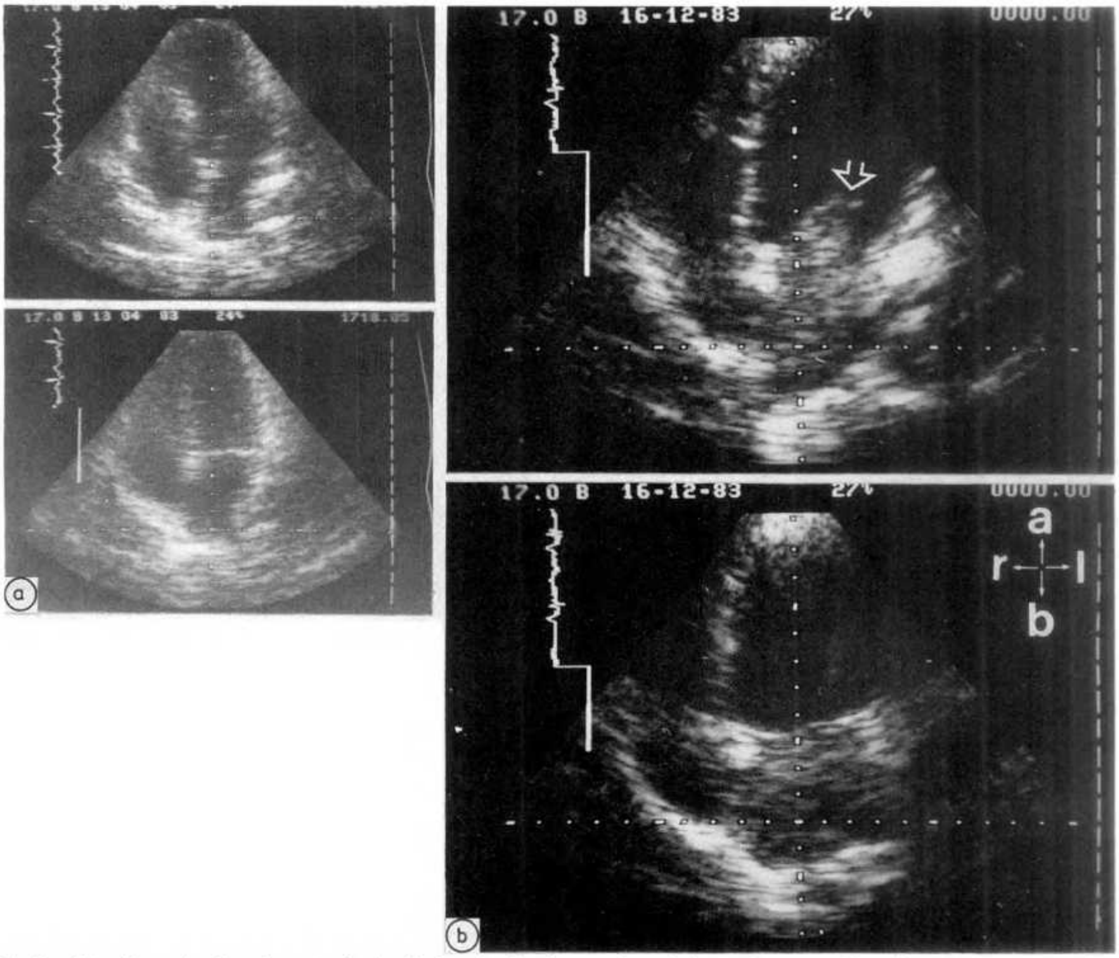

Fig 2 *Apical four chamber views. (a) In April when the chamber was free of abnormal masses. (Top, diastole; bottom, systole). Left cavities are on the right. (b) Eight months later a large mass was seen in the left atrium during systole (bottom). During diastole the mass protruded through the mitral valve into the left ventricular inflow tract (top). (a, apex; b, base; r, right; l, left).*

Discussion

The time taken for an atrial myxoma to produce symptoms is variable.$^{2-4}$ To our knowledge this is the first well documented case of rapid growth of an atrial myxoma. Cases of rapid recurrence of left atrial myxoma have been reported, however. St John Sutton *et al* reported two tumour recurrences within three years of myxoma resection.[1] Read *et al* reported two recurrences of the tumour in the same patients[5]; the first myxoma was attached to the interatrial septum and was excised and the first recurrence (from the left posterolateral atrial wall) occurred 15 months after resection. Because the base of the second tumour could not be removed completely it was cauterised. Seven months after the second operation there was a second recurrence from the previously cauterised base. Read *et al* concluded that partial excision was the most likely cause of recurrence but that rapid recurrence does not always follow incomplete resection.[6]

Some workers have described rapid symptomatic deterioration probably caused by haemorrhage within the rapidly enlarging myxoma.[7] In our experience of 26 atrial myxomas we found only one recurrence; this occurred seven years after the initial resection.

Cross sectional echocardiography should be repeated if new clinical features develop that are compatible with an intracardiac tumour. Multiple views were recorded during each examination in the present case. We believe that the tumour was too small to be seen at the first examination. The tumour in our case was unusually vascular. Increased vascularity is also found in cases of left atrial thrombi.[8] Some workers believe that highly vascularised myxomas may be difficult to diagnose by echocardiography because their echogenicity is low.[9] In our case, however, vascularisation of the left atrium was not abnormal on the first coronary angiogram in April and when the tumour was discovered by cross sectional echocardiography the following December the mass showed considerable homogeneous echogenicity.

We thank Professor F Fontan and Dr N Sourdille for their contributions to this study and Professor A de Mascarel and Dr J F Goussot, Service d'Anatomopatholgie, Hôpital St André, 33000 Bordeaux, who performed the histological examination.

References

1 St John Sutton M, Mercier LA, Giuliani ER. Atrial myxoma: a review of clinical experience in 40 patients. *Mayo Clin Proc* 1980;**55**:371–6.

2 Oldershaw PJ, St John Sutton M, Gibson RV. Long asymptomatic period of atrial myxomas. *Thorax* 1980:35:70–9.

3 Bulkley BH, Hutchins GM. Atrial myxoma: a fifty year review. *Am Heart J* 1979;**97**:639–43.

4 Croxson RS, Jewitt D, Bentall HH, Cleland WP, Kristinsson A, Goodwin JF. Long-term follow up of atrial myxoma. *Br Heart J* 1972;**34**:1018–23.

5 Read RC, White HJ, Murphy MC, Williams D, Sun CN, Flanagan WH. The malignant potentiality of left atrial myxoma. *J Thorac Cardiovasc Surg* 1974;**68**:857–68.

6 Richardson JU, Brandt B, Doty DB, Ehrenhaft JL. Surgical treatment of atrial myxomas: early and late results of 11 operations and review of the literature. *Ann Thorac Surg* 1979;**28**:354–8.

7 Pandian NG, Isner JE, McInerney KP, Caldeira ME, Donaldson RF. Left atrial myxoma. Implications of site, size, mobility and tissue structure. *Echocardiography* 1985;**2**:113–8.

8 Shapiro MR, Cohen MV, Grose R, Spindola-Franco H. Diagnosis of left atrial myxoma by coronary arteriography eight years following open mitral commissurotomy. *Am Heart J* 1983;**15**:325–7.

9 Come PC, Riley MF, Markis JE, Malagold M. Limitations of echocardiographic technique in evaluation of left atrial masses. *Am J Cardiol* 1981;**48**:947–53.

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Variant angina induced by biliary colic

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SUMMARY A 65 year old woman with gall stones presented with crushing chest pain after an attack of biliary colic. The electrocardiogram showed ST segment elevation in leads I, aVL, and V1–V3 while leads II, III, and aVF showed ST segment depression. Cardiac enzyme activity remained within the normal range. During the next three weeks attacks of epigastric and right hypochondrial pain preceded by crushing chest pain with identical electrocardiogram changes occurred with decreasing frequency. Coronary arteriography showed 60% obstruction of the left anterior descending coronary artery and good left ventricular function. During the next three years the patient complained both of mild abdominal pain, probably biliary colic, and mild effort related angina pectoris without a relation between the two symptoms.

It is suggested that the attack of variant angina was triggered by biliary colic through sympathoadrenal discharge causing vasospasm.

Variant angina pectoris is characterised by recurring attacks of chest discomfort at rest associated with ST segment elevation on the electrocardiogram. ST segment changes disappear as the pain subsides and there is no evidence of myocardial necrosis. Various stimuli have been reported to induce variant angina[1]; we describe a case of variant angina pectoris precipitated by biliary colic.

Case report

A 65 year old woman was admitted to our department with crushing left chest pains radiating to the neck. These followed intense spasmodic pain in the epigastrium and right hypochondrium radiating to the right shoulder. During the year before admission she had occasional attacks of mild right upper quadrant pain precipitated by fatty meals which were diagnosed as biliary colic; oral cholecystography showed gall stones.

On admission the patient was pale and sweating; her blood pressure was 140/80 mm Hg, the pulse was regular 80 beats/min, and she weighed 82 kg. There was acute tenderness at the upper abdomen; a fourth heart sound was audible on the precordium; the remainder of the examination was unremarkable. Chest *x* ray was normal. The electrocardiogram showed sinus rhythm, T wave inversion in leads V2–V4 (fig 1a). Laboratory data were as follows: creatine kinase 2·4 μkat/l (normal value < 1·6), alanine aminotransferase 0·66 μkat/l (normal < 0·37), aspartate aminotransferase 0·37 μkat/l (normal < 0·42), serum bilirubin 36 μmol/l (indirect 13·7 μmol/l), haemoglobin 142 g/l, haematocrit 43%, and a white cell count 10 500 with a normal differential count.

The day after admission she complained of spasmodic pain in the epigastrium and right hypochondrium; some while after, the pain worsened and radiated to the right posterior region of the thorax: the electrocardiogram showed sinus rhythm and biphasic T waves in leads V2–V4 (fig 1b). About 20 minutes later an intense oppressive chest pain developed, radiating to the neck, while the electrocardiogram showed sinus rhythm 74 beats/minute, ST segment elevation in leads I, aVL, and V1–V3 with ST segment depression in leads II, III, and aVF (fig 1c). The spasmodic epigastric and hypochondrical chest pain gradually disappeared after half an hour and the electrocardiographic pattern returned to that observed on admission (fig 1d); twelve hours later an electrocardiogram revealed biphasic T waves in leads V2–V4 (fig 1e). Cardiac enzyme activities remained in the normal range.

She was started on nifedipine (60 mg daily). The next day she had another attack of biliary colic angina with similar ST segment elevation on the electrocardiogram and papaverine (80 mg three times a day and verapamil (80 mg) three times a day were added to the treatment. In the next three weeks she complained of other attacks, but these declined in duration and intensity and the degree of ST seg-

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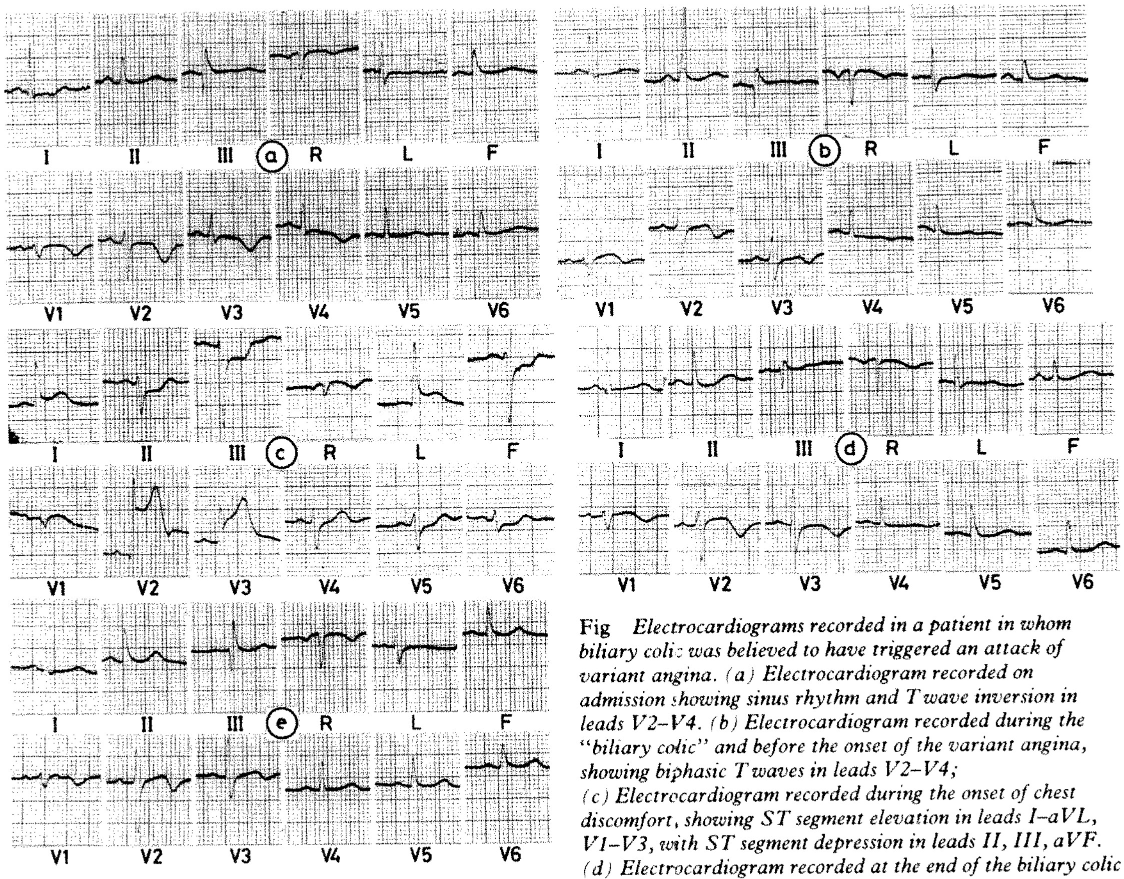

Fig *Electrocardiograms recorded in a patient in whom biliary colic was believed to have triggered an attack of variant angina. (a) Electrocardiogram recorded on admission showing sinus rhythm and T wave inversion in leads V2–V4. (b) Electrocardiogram recorded during the "biliary colic" and before the onset of the variant angina, showing biphasic T waves in leads V2–V4; (c) Electrocardiogram recorded during the onset of chest discomfort, showing ST segment elevation in leads I–aVL, V1–V3, with ST segment depression in leads II, III, aVF. (d) Electrocardiogram recorded at the end of the biliary colic angina attack, showing a T wave inversion in leads V2–V4. (e) Electrocardiogram recorded twelve hours after the attack of biliary colic and angina, showing biphasic T waves in leads V2–V4.*

ment elevation also lessened. Cardiac enzyme activities remained in the normal range.

A month after admission the T waves in leads V2–V4 became positive and cardiac catheterisation revealed 60% obstruction of the left anterior descending coronary artery and good left ventricular function. The patient felt well and was discharged.

In the next three years she continued to complain of angina pectoris on effort (functional group New York Heart Association II) and of mild pain in the right upper quadrant, which was probably biliary. The occurrence of these two symptoms was unrelated. The patient refused cholecystectomy and continued taking calcium antagonists.

Discussion

In our patient the onset of the chest pain at rest, the typical electrocardiographic changes, and the lack of evidence of myocardial necrosis justify the diagnosis of variant angina pectoris; however, the presence of a 60% narrowing in the left anterior descending coronary artery suggests that it was mixed rather than classic variant angina. In this patient biliary colic caused a cramping pain in the right upper quadrant that radiated to the right posterior region of the thorax, whereas cardiac ischaemia caused a crushing pain in the left chest that radiated to the neck. Moreover, the pattern of the electrocardiogram during the biliary colic and before the onset of the chest discomfort was similar to that recorded during the pain free period. The temporal relation suggests that the onset of biliary colic triggered the variant angina.

Coronary artery spasm[2] causes variant angina pectoris; but the mechanism by which it occurs remains unclear. It usually occurs at the site of an atherosclerotic lesion[3] and the normal mechanism by which the endothelium counteracts vasospasm has been compromised.[4]

Coronary arteries are innervated by both sympathetic and parasympathetic nerves, both α_1 (vasoconstrictor) and β_1 (vasodilator) adrenoceptors are present in the large vessels but the β_1 adrenoceptors predominate functionally; in the branch arteries only β_1 adrenoceptors are present: α_2 adrenoceptors and muscarinic receptors are present on the sympathetic nerve endings of the coronary arteries; their activation reduces the release of noradrenaline and hence lessens the dilatation of these vessels.

Both parasympathetic[5] or α adrenergic[6 7] stimulation can precipitate coronary vasoconstriction. A relation between spasm of the coronary artery and spasm of the oesophagus was found in some patients and the stimulation of α adrenergic receptors was suggested as the common pathogenetic mechanism.[8] We think that in our patient the sympathoadrenal discharge accompanying biliary colic could have triggered the α adrenoceptors causing coronary vasospasm that resulted in an attack of angina.

References

1 Takizawa A, Yasue H, Omote S, *et al*. Variant angina induced by alcohol ingestion. *Am Heart J* 1984;**107**:25–7.

2 Maseri A, Severi S, De Nes M, *et al*. Variant angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia. *Am J Cardiol* 1978;**42**:1019–35.

3 Dalen JE, Ockene IS, Alpert JS. Coronary spasm, coronary thrombosis, and myocardial infarction. *Am Heart J* 1982;**104**:1119–24.

4 Shepherd JT, Van Houtte PM. Mechanism responsible for coronary vasospasm. *J Am Coll Cardiol* 1986;**8**:50A–4A.

5 Yasue H, Touyama M, Shimanoto M, Kato H, Tanaka S, Akiyama F. Role of autonomic nervous system in the pathogenesis of Printzmetal's variant form of angina. *Circulation* 1974;**50**:534–9.

6 Yasue H, Touyama M, Kato H, Tanaka S, Akiyama F. Printzmetal's variant form of angina as a manifestation of alpha-adrenergic receptor-mediated coronary artery spasm: documentation by coronary arteriography. *Am Heart J* 1976;**91**:148–55.

7 Winniford MD, Wheelan KR, Kremers MS. Smoking induced coronary vaso-constriction in patient with atherosclerotic coronary artery disease: evidence for adrenergically mediated alterations in coronary artery tone. *Circulation* 1986;**73**:662–7.

8 Rasmussen K, Funch-Jensen P, Ravensbaek J, Bagger JP. Oesophageal spasm in patients with coronary artery spasm. *Lancet* 1986;**i**:174–6.

Br Heart J 1987;58:420–1

Correspondence

Reversibility of primary pulmonary hypertension during six years of treatment with oral diazoxide

Sir,
We were interested to see the report by Chan *et al* (1987;57:207–9). In 1981 we described a patient with primary pulmonary hypertension who went into a complete remission after treatment with oral diazoxide.[1] The drug was stopped after 15 months because of side effects and the pulmonary hypertension returned. Diazoxide was recommenced and the patient has remained well and symptom free since. It is now nine years since she originally presented. Although her pulmonary artery pressure has not been measured recently she is clinically in remission. There is slight elevation of the venous pressure and the right ventricle is easily palpable. There is a soft ejection systolic murmur in the pulmonary area and a loud pulmonary second sound. The chest radiographs show slight prominence of the main pulmonary artery but a normal heart size. There has been considerable improvement in the radiographic appearances since presentation and the electrocardiographic changes of right ventricular hypertrophy have resolved. Her only other treatment has been warfarin with chlorpropamide and diuretics for side effects of the diazoxide.

We are convinced that the improvement in our patient's condition is the result of diazoxide treatment and we intend to continue the drug indefinitely. The publication of this further case supports our view that vasodilator drugs should be considered in all patients with primary pulmonary hypertension.

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Cambridge.

Reference

1 Hall DR, Petch MC. Remission of primary pulmonary hypertension during treatment with diazoxide. *Br Med J* 1981;282:1118.

Viral myocarditis and dilated cardiomyopathy in early childhood

Sir,
I read with interest the paper by Weinhouse *et al* (1986;56:94–7) describing the value of serial echocardiography in the follow up of infants and children with dilated cardiomyopathy. While agreeing with the value of such investigations, I remain concerned that the evidence for a viral myocarditis as the explanation of the dilated cardiomyopathy was somewhat incomplete. Viruses were grown from four of their 10 patients while in one an antibody titre suggested a recent infection. They indicated that all 10 infants had histories compatible with previous viral illnesses.

While I accept that it is very difficult to be certain of a viral aetiology in such patients,[1] it is essential to exclude potentially treatable conditions. Other workers have emphasised the importance of looking carefully for an anomalous left coronary artery arising from the pulmonary trunk.[2 3] Echocardiographic evidence and the use of other non-invasive techniques have at times proved inconclusive. Direct visualisation of the coronary arteries at aortography remains essential. Endomyocardial biopsy may sometimes provide information that is not obtainable in any other way. For example, we recently had a child admitted in severe cardiac failure, from whom a Coxsackie A virus was grown from a throat swab. She subsequently was shown on endomyocardial biopsy to have iron infiltration of the myocardium consistent with idiopathic haemochromatosis. She has responded well to repeated venesection. Leatherbury *et al* reported the value of such biopsies, which changed the diagnosis in 38% of their 16 patients, 14 of whom presented with a clinical diagnosis of dilated cardiomyopathy or myocarditis.[4]

Samuel Menahem,
Department of Cardiology,
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Melbourne, Australia.

References

1 Menahem S, Uren E. Respiratory syncytial virus and heart block—cause and effect. *Aust NZ J Med* 1985;**15**:85–7.
2 Robinson PJ, Sullivan ID, Kumpeng V, Anderson RH, Macartney FJ. Anomalous origin of the left coronary artery from the pulmonary trunk. Potential for false negative diagnosis with cross sectional echocardiography. *Br Heart J* 1984;**52**:272–7.
3 Menahem S, Venables AW. Anomalous left coronary artery from the pulmonary artery: a 15 year sample. *Br Heart J* 1987;**58**;378–84.
4 Leatherbury L, Chandra RS, Shapiro SR, Bradley LM. Endomyocardial biopsies in children [Abstract]. *J Am Coll Cardiol* 1986;**5**:406.

Br Heart J 1987;58:422

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British Cardiac Society

The Golden Jubilee Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987

The meeting will be chaired by Donald Ross. In the first of two plenary sessions entitled "Great British Cardiologists of the Past":

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Edwin Besterman on A D Waller;
Arthur Hollman on Sir Thomas Lewis;
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Walter Somerville on Paul Wood;
Donald Ross on Lord Brock.

The second plenary session is "Cardiology—the Future" in which the chairmen of all the working parties will participate:

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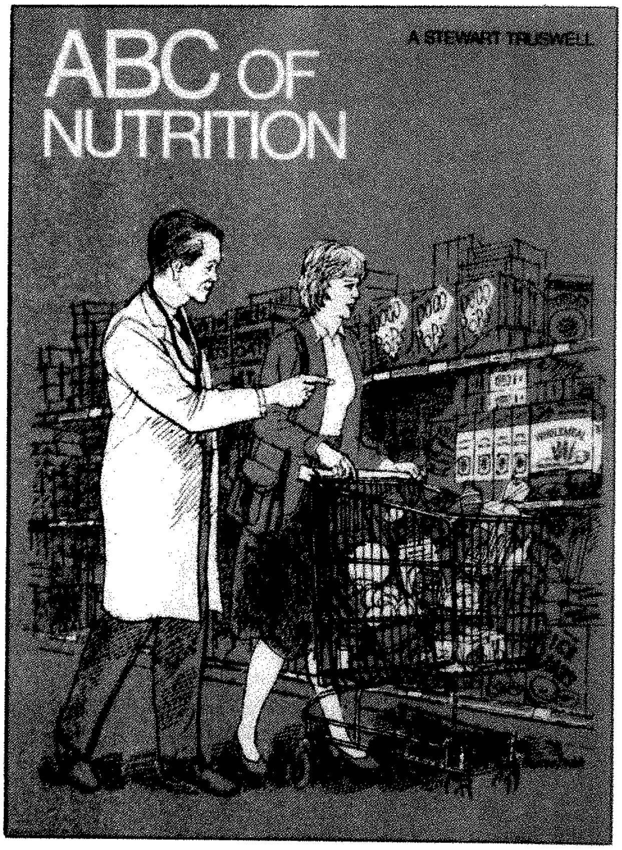

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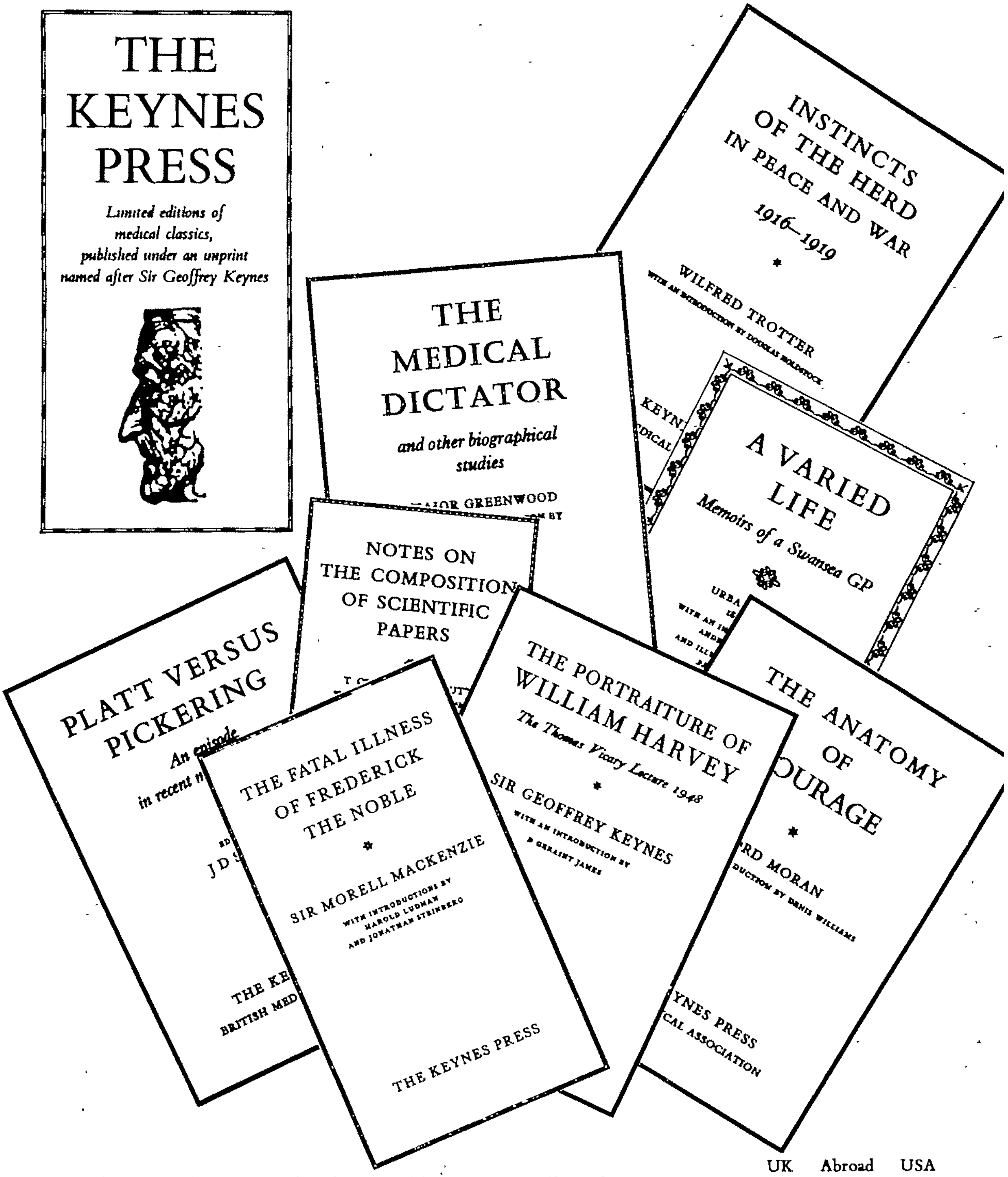
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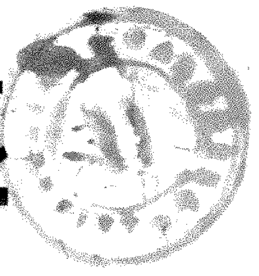

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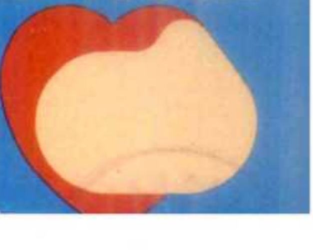

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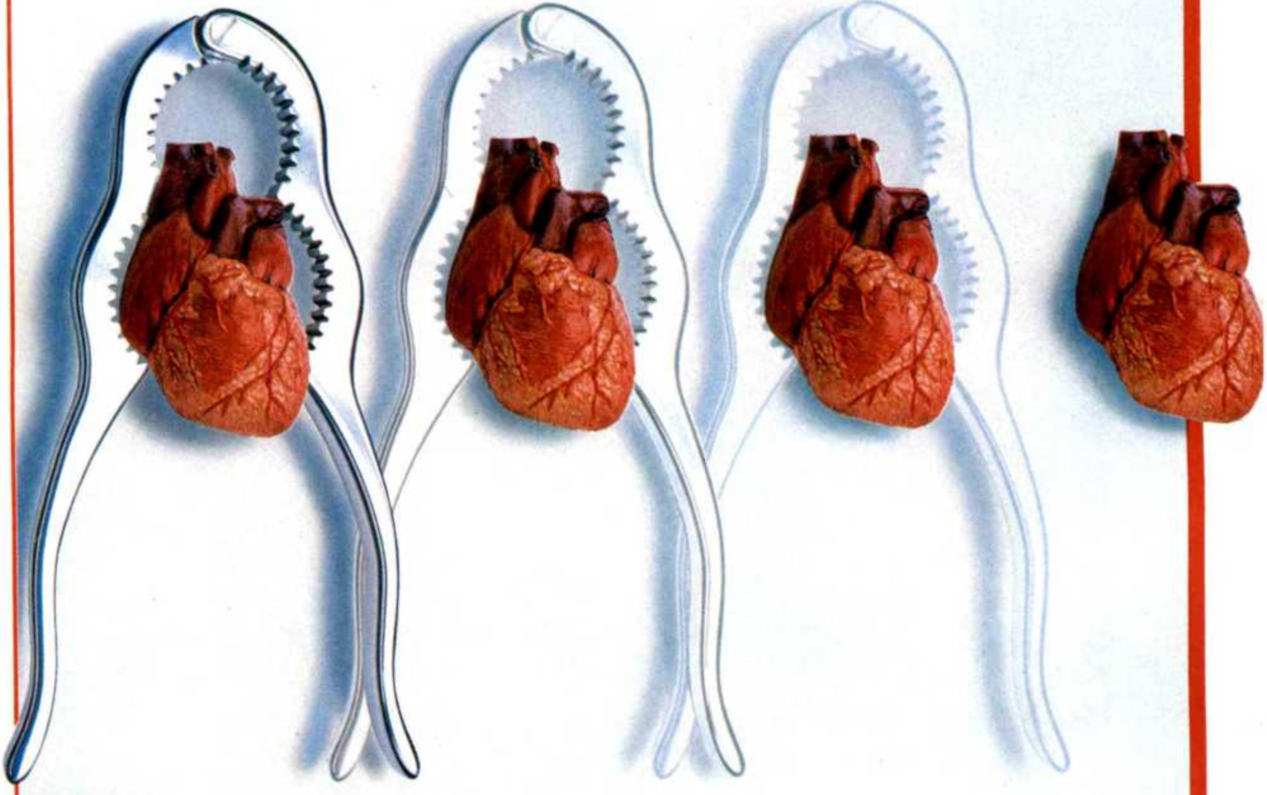

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Jubilee Editorial

The medical treatment of angina pectoris

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Fifty years ago, the treatment of angina pectoris made no strong claim for space in journals of cardiology. In January 1939 Maurice Campbell submitted the first article on angina to be published in the *British Heart Journal*,[1] but it was no more than a case report. Five years were to pass before a paper on treatment appeared, written by Wilfred Stokes.[2] He reported an investigation of the value of nicotinic acid in this condition but concluded that the drug did not improve either the prevention or relief of pain. The first and last sentences of the article were similar: both stated that glyceryl trinitrate had no equal in the treatment of angina pectoris—a contention that remained true and mostly unchallenged well into the professional lives of many cardiologists practising today.

The new era of treatment

The therapeutic breakthrough came with the introduction into clinical medicine of β adrenergic blockade: there was no fanfare, but the new class of drugs was recognised as important enough to merit three papers in a single issue of the *Lancet*, one of which included the first account of pronethalol in the treatment of angina.[3] By the time this first clinical agent was found to be unacceptable because of its toxicity[4] others were available to take its place.[5] Despite the obsessive care in drug registration by the Food and Drug Administration that held back progress in the United States for nearly 10 years, β blockade rapidly became an established treatment. When verapamil was introduced, the antianginal effects of this powerful drug were not recognised at first as being the result of a novel type of action. There was, indeed, a celebrated correspondence in the *Lancet*[6] in which notable experts debated whether the efficacy of verapamil was due principally to its actions as a β blocker—by then the passport to respectability. But the calcium channel antagonists have come of age, with a plethora of agents that show more pharmacodynamic diversity than the β adrenergic blockers. We have also acquired sustained action nitrates of proven efficacy, and we have the possibility of widening horizons for intervention together with a bewildering number of drug combinations.

The introduction of β blockers

The introduction of β adrenergic antagonists owed nothing to serendipity, which is so often the father of progress. During the late 1950s, Black (later Sir James) started his quest for a method of sparing myocardial oxygen demand by attenuating the effects of sympathetic drive on the heart, and led his colleagues in the pharmaceutical industry in the development of analogues of isoprenaline that would block the β receptors,[7] the very existence of which had been postulated only a few years before.[8] He was not the first to produce such a compound: scientists at the Eli Lilly laboratories had already developed dichloroisoprenaline[9] which had become a useful pharmacological tool that first stimulates but then blocks the β receptors. But the clinical potential of β blockade was not seen by the earlier workers. Others, however, were awakening to the value of inhibiting sympathetic influences on the heart. At St Bartholomew's Hospital, sympathectomy was a relatively common treatment for angina during the late 1950s; Hayward and Apthorp were particularly interested in the improvement in effort tolerance that accompanied surgical interruption of the pain fibres. They exercised patients on a treadmill to look for evidence of dangerous ischaemia that might be masked postoperatively. They reported, however, evidence of an improvement in myocardial performance and showed that abnormalities in the electrocardiogram recorded after effort could be abolished or delayed by surgery.[10] As a newly fledged research registrar bereft of a project, after the untimely death of Weitzman in the same department, I decided to

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investigate this phenomenon and concluded first that it must be due to interruption of the afferent (motor) sympathetic fibres rather than to pain control, and secondly that it should be possible to reproduce the effect with dichloroisoprenaline or a similar agent. Many months of correspondence with Eli Lilly followed, and a supply of dichloroisoprenaline (with a disclaimer of responsibility) came two days before the publication of the first *Lancet* papers by Black and his colleagues. Only the correspondence and a generous attribution by one of the other early workers who had read the letters[11] remained to sustain my unrealistic pipedream of fame.

Mechanisms of action of β blockers

The mechanisms of action of β blockade in angina are now well known, and can be most easily understood in the context of the concept of the supply and demand of energy for the work of the heart.[12] On the demand side of the equation, heart rate and energy-wasting contractility are reduced, while the reduction in free fatty acid concentration may force myocardial metabolism towards greater dependence on carbohydrate metabolism that is more economical in terms of oxygen use. Wall tension is another factor that may decrease in response to a reduction in blood pressure, but this can be countered by any appreciable dilatation of the heart as a result of β blockade[13] which changes the relation between tension in the ventricular wall and intracavity pressure. On the other side of the equation, the potential for the supply of energy will be favoured by the longer diastolic filling time after β blockade, but perfusion pressure may be augmented less during exercise; the effects on the tone of coronary vessels are contentious and probably variable. Thus not all effects are favourable and individuals vary in the degree to which symptoms improve.

The effect of β blockade on the mortality of angina is unknown and unlikely ever to be tested in a formal clinical trial because the use of a control group deprived of agents of so much symptomatic value has never been appropriate. This is unfortunate because other drugs of comparable efficacy for relief of angina are now available. A few facts may be worth pondering, however, when considering guidelines for treatment: first, the mortality in patients with angina in the United States improved at about the time β blockers were introduced[14]; secondly, one trial in general practice did show an appreciable reduction in mortality in patients on β blockers; however, allocation to the treatment and control groups was not based on an acceptable randomisation procedure[15]; thirdly, protection by some agents has been demonstrated during the convalescent phase after infarction.[16] This is hardly compelling evidence for the contention that β blockers save life in patients with angina, but taken in association with evidence of a protective effect against arrhythmias in animal models[17] and the symptomatic relief they provide, we should continue to regard them as the sheet-anchor of treatment for most patients in the forseeable future.

Calcium antagonists

The introduction of calcium antagonists into clinical medicine also followed research in basic physiology. The concept was pioneered and developed by Fleckenstein *et al.*[18] It now embraces agents of widely different structure and with pharmacological effects both at membrane level (calcium entry blockers) and within cells. The criteria for inclusion of substances as calcium antagonists are not agreed, and the classification in some recent reviews is complex.[19] The drugs of greatest interest in cardiology are the entry blockers that are selective and influence the slow calcium channels of the myocardium and arteries—including the coronary arteries. Their pharmacological activity depends at least in part on limiting the binding of calcium to calmodulin within smooth muscle; calcium calmodulin activates myosin light-chain kinase which phosphorylates myosin, and this in turn promotes contractile activity.[20]

The drugs licensed for use in the United Kingdom have a range of activity: verapamil has the most effect on myocardial contractility and on the activity of the sinus and atrioventricular nodes, while nicardipine has the least direct action on the heart and greatest relative effect on vascular (including coronary) tone. Nifedipine resembles nicardipine and from a clinical viewpoint is similar; diltiazem is near the middle of the spectrum with important actions of both types.

What are the clinical implications of these differences in the actions of calcium channel blockers? In summary, verapamil is a powerful antianginal agent that at least matches β blockers in efficacy as a single agent for the treatment of anginal syndromes caused by obstructive coronary disease.[21 22] But it must be used with caution because its negative inotropic effect can precipitate heart failure[23] and its effect on the conducting system can cause sinoatrial block, atrioventricular block, and asystole.[24] Because of the resemblance to the adverse effects of β blockade (mediated by mechanisms that are different yet complementary) the high risk of combination treatment[25 26] should cause no surprise. It can be used successfully, however, in patients with coincident bronchospasm and symptomatic peripheral vascular disease. Towards the other end of the spectrum, nifedipine is a safe drug with unwanted effects that can be very unpleasant[27] yet are reversible and hardly ever life threatening; nicardipine may share this advantage. The special role of these two drugs lies in the prophylaxis of variant or vasospastic angina, but they are not the agents of first choice for the treatment of exertional angina unless others are contraindicated. Unlike verapamil, however, they are useful in combination with β blockers, since reduction in afterload may be of value and many patients with obstructive disease do have symptoms caused by inappropriate coronary tone or spasm.[28] Diltiazem has a broader range of efficacy than other agents because of its more central position on the calcium antagonist spectrum, though it is unlikely to be as effective as verapamil for syndromes that are dominantly obstructive nor as effective as nifedipine or nicardipine for syndromes that are dominantly vasospastic. Its value lies in its therapeutic versatility, its relative safety compared with verapamil, and in the smaller risk of its use in association with β blockers.

The nitrates

Glyceryl trinitrate is the oldest of the present day drugs used to control angina; it was first used to treat migraine.[29] The image of the nitrates has been freshened by the relatively recent demonstration that oral treatment can provide sustained effects,[30 31] by the introduction of new methods of administration,[32-34] and by advances in our knowledge of their mechanism of action. Controversy continues about the value of sustained action in this class of compounds. While this is clearly a desirable therapeutic goal, it carries the risk that efficacy may be negated by the tolerance which develops so readily with nitrates. Short term studies can show impressive persistence of the antianginal effect of isosorbide dinitrate in a range of doses for up to eight hours after dosing,[31] but with long term treatment, with doses four times a day, tolerance does develop and some efficacy is lost.[35] For this reason, some have doubted the value of nitrates in regular drug regimens to control angina and have restricted their use to sublingual preparations for short lived relief.

Recent studies suggest that long acting nitrates are important in prophylaxis. Tolerance occurs particularly in response to the persistence of a threshold concentration of nitrates in the body, and it is greatly mitigated by even brief "nitrate free" periods during the 24 hour day. Thus no tolerance was noted when oral isosorbide dinitrate was given for a month at 8 am and 1 pm.[36] In tests lasting a week, exercise time was improved for only an hour after dosing four times daily but for five hours if doses were restricted to three times a day.[37] For patients with daytime effort angina, Parker has suggested that treatment incorporating the administration of long acting oral nitrates three times a day may be appropriate provided the last dose is taken with an early evening meal rather than at bedtime.[38] The theoretical risk of rebound coronary constriction, similar to that experienced as nitrate concentrations fell in workers with occupational exposure[39] has not become apparent in the clinical evaluation of these agents.

The mechanism of action of nitrates is not yet fully understood but knowledge is unfolding rapidly. They confer benefit in patients with angina with more consistency than any other class of agent, yet their effects on the systemic circulation seem not to be wholly beneficial. In particular the tachycardia induced by nitrates must be unfavourable both in terms of energy demands by the myocardium and the metabolic supply to it. Clinicians must often have been puzzled as they saw the rapid relief of pain despite increasing heart rate in their patients, and sometimes at least must have wondered what unrecognised benefits may be occurring. Appreciation that all was not understood has been reflected in a grumbling controversy on how far relief from angina accrued from systemic effects and how far from effects on the coronary circulation. The pendulum, once firmly on the systemic side, has moved recently to a more central position with the recognition that the pathophysiology of angina forms a continuum with obstructive disease at one end and spasm at the other; the syndrome in most subjects occupies a position somewhere in between. Increased coronary tone may contribute in a recognisable fashion to the pattern of angina,[40] it may increase paradoxically and harmfully as ischaemia develops,[28] and it may account for variation in effort tolerance—as shown for example in the second wind phenomenon.[41] Nitrate induced coronary vasodilatation at the site of this potential increase in tone must complement the systemic effects[28] which have never seemed an adequate explanation for the mechanism of such an effective drug.

At a cellular level the theories that are propounded must take account of the propensity of these drugs to produce tachyphylaxis during continuous administration and a subsequent rapid recovery from this response. Nitrates may work after conversion to nitric acid or nitric oxide which is then converted to nitrosothiols by reacting with the sulphydryl compounds in vascular smooth muscle.[42] These nitrosothiols in turn stimulate guanylate cyclase and increase production of guanosine monophosphate which reduces calcium entry into the muscle cell. The possible relation with conventional calcium channel blockers is evident, but it should be noted too that nitric oxide has recently been identified as endothelium derived relaxing factor.[43] This factor is present in intact endothelium and can be released by acetyl choline. It is believed to mediate some physiological vasodilatation, and already there is evidence that defects in the mechanism have a role in disease.[44]

In 50 years the wheel has turned full circle and nitrates are once again a focus of interest. No longer the only effective agents as in Stokes's time, they now are central to an attractive unified hypothesis for physiological and pharmacological mechanisms of coronary vasodilatation. Many therapeutic agents must interact with the chain of events extending from nitric oxide and endothelium derived relaxing factor to the calcium entry that controls coronary vasomotor tone. Nitrates, indeed, may resemble opiates in being therapeutic agents of long standing that owe their potency to a chemical relation with substances used in natural control mechanisms.

Other antianginal agents

Some drugs with proven efficacy in angina do not fit easily into the classification comprising nitrates, β blockers, and calcium antagonists. The most notable is perhexiline maleate which was undoubtedly a most useful agent before it was withdrawn by the manufacturers. The most serious unwanted effects occurred particularly in people with defective hepatic hydroxylation,[45] which affects the rate of metabolism of many drugs, but the benefits were impressive in most patients with exercise induced angina. The drug has some calcium channel blocking activity though it has no negative inotropic effect. The antianginal action probably depends on the diversion of myocardial metabolism from fatty acid substrates to the more oxygen-sparing carbohydrates.[46] We lack an alternative agent of this type, and many regret that perhexiline can no longer be used as a secondary drug for patients with refractory angina. Harm is unlikely if plasma concentrations are controlled and an assay is available.[47]

The next 50 years

What of the future? We cannot foretell the path of progress over the next 50 years, but in the foreseeable future we may have agents that will modify more specifically the effects of sympathetic influences on coronary tone perhaps by α blockade, we will certainly have useful adrenoceptor blockers that are partial agonists, a plethora of new calcium antagonists, and perhaps new agents with actions that modify myocardial metabolism. We can be reasonably optimistic that the longer term will bring greater understanding of the pathogenesis of atheroma, the ability to control both its progession and its complications, and ultimately agents to promote its regression. The next jubilee editorial in the *British Heart Journal* on the medical treatment of angina would then be predominantly a historical review.

References

1 Campbell M. Angina pectoris following a crushing accident. *Br Heart J* 1939;1:177–80.
2 Stokes W. Nicotinic acid in the treatment of angina pectoris. *Br Heart J* 1944;6:157–60.
3 Dornhorst AC, Robinson BF. Clinical pharmacology of a beta-adrenergic-blocking agent (nethalide). *Lancet* 1962;ii:314–6.
4 Alcock SJ, Bond PA. Observations on the toxicity of Alderlin (pronethalol) in laboratory animals. *Proc Eur Soc Study Drug Toxicol.* In: Excerpta Medica Foundation ICS 1964;81:30–7.
5 Black JW, Crowther AF, Shanks RG, Smith LH, Dornhorst AC. A new adrenergic beta-receptor antagonist. *Lancet* 1964;i:1080–1.
6 Bateman FJA. What is a β-blocker? [Letter]. *Lancet* 1967;ii:418.
7 Black JW, Stephenson JS. Pharmacology of a new adrenergic beta-receptor-blocking compound (nethalide). *Lancet* 1962;ii:311–4.
8 Ahlquist RP. A study of the adrenotropic receptors. *Am J Physiol* 1948;153:586–600.
9 Powell CE, Slater IH. Blocking of inhibitory adrenergic receptors by a dichloro analog of isoproterenol. *J Pharmacol Exp Ther* 1958;122:480–8.
10 Apthorp GH, Wedgwood J, Hayward GW. The objective assessment of the results of sympathectomy for angina: the effect of sympathectomy on pain and ECG evidence of myocardial ischaemia during exercise. Proceedings of the Third European Congress of Cardiology. Rome: Pars Altera, 1960:51.
11 Shanks RG. The properties of beta-adrenoceptor antagonists. *Postgrad Med J* 1976;52(suppl 4):14–20.
12 Sonnenblick EH, Ross J Jr, Covell JW, Braunwald E. Velocity of contraction as a determinant of myocardial oxygen consumption. *Am J Physiol* 1965;209:919–27.
13 Chamberlain DA. Effects of beta adrenergic blockade on heart size. *Am J Cardiol* 1966;18:321–5.
14 Read RC, Murphy ML, Hultgren HN, Takaro T. Survival of men treated for chronic stable angina pectoris. A cooperative randomized study. *J Thorac Cardiovasc Surg* 1978;75:1–12.
15 Lambert DMD. Effect of propranolol on mortality in patients with angina. *Postgrad Med J* 1976;52(suppl 4):57–60.
16 Chamberlain DA. Beta adrenoceptor antagonists after myocardial infarction—where are we now? *Br Heart J* 1983;49:105–10.
17 Han J, Garcia de Jalon P, Moe GK. Adrenergic effects

on ventricular vulnerability. *Circ Res* 1964;**14**: 516–24.

18 Fleckenstein A, Tritthart H, Fleckenstein B, Herbst A, Grun G. Eine neue Gruppe kompetitiver Ca^{++} Antagonisten (Iproveratril, D600, Prenylamin) mit starken Hemmeffekten auf die elektromekanische Koppelung im Warmblüter-myokard. *Pflügers Arch* 1969;**307**:R25.

19 Godfraind T. Classification of calcium antagonists. *Am J Cardiol* 1987;**59**:11B–23B.

20 Adelstein RS, Sellers JR. Effects of calcium on vascular smooth muscle contraction. *Am J Cardiol* 1987;**59**:4B–10B.

21 Livesley B, Catley PF, Campbell RC, Oram S. Double-blind evaluation of verapamil, propranolol, and isosorbide dinitrate against a placebo in the treatment of angina pectoris. *Br Med J* 1973;**i**:375–8.

22 Parodi O, Simonetti I, Michelassi C, *et al.* Comparison of verapamil and propranolol therapy for angina pectoris at rest: a randomized, multiple-crossover, controlled trial in the coronary care unit. *Am J Cardiol* 1986;**57**:899–906.

23 Chew CYC, Hecht HS, Collett JT, McAllister RG, Singh BN. Influence of severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. *Am J Cardiol* 1981;**47**:917–22.

24 Hagemeijer F. Verapamil in the management of supraventricular tachyarrhythmias occurring after a recent myocardial infarction. *Circulation* 1978;**57**:751–5.

25 Packer M, Leon MB, Bonow RO, Kieval J, Rosing DR, Subramanian VB. Hemodynamic and clinical effects of combined verapamil and propranolol therapy in angina pectoris. *Am J Cardiol* 1982;**50**:903–12.

26 Krikler DM, Spurrell RAJ. Verapamil in the treatment of paroxysmal supraventricular tachycardia. *Postgrad Med J* 1974;**50**:447–53.

27 Anonymous. Nifedipine for angina pectoris. *Med Lett Drugs Ther* 1982;**24**:39–41.

28 Gage JE, Hess OM, Murakami T, Ritter M, Grimm J, Krayenbuehl HP. Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: reversibility by nitroglycerin. *Circulation* 1986;**73**:865–76.

29 Field AG. On the toxical and medicinal properties of nitrate of oxyde of glycyl. *Med Times Gazette* 1858,**16**:291–2.

30 Lee G, Mason DT, De Maria AN. Effects of long-term oral administration of isosorbide dinitrate on the antianginal response to nitroglycerin; absence of nitrate cross-tolerance and self-tolerance shown by exercise testing. *Am J Cardiol* 1978;**41**:82–7.

31 Thadani U, Fung H-L, Darke AC, Parker JO. Oral isosorbide dinitrate in the treatment of angina pectoris. dose-response relationship and duration of action during acute therapy. *Circulation* 1980;**62**:491–502.

32 Abrams J. New nitrate delivery systems: buccal nitroglycerin. *Am Heart J* 1983;**105**:848–54.

33 Reichek N, Goldstein RE, Redwood DR, Epstein SE. Sustained effects of nitroglycerin ointment in patients with angina pectoris. *Circulation* 1974;**50**:348–52.

34 Chevigne M, Renier J, Rigo P, Demoulin P, Collignon P, Kulbertus HE. Efficacité de la nitroglycérine en nébuliseur. *Rev Med Interne* 1980;**1**:265–72.

35 Thadani U, Fung H-L, Darke AC, Parker JO. Oral isosorbide dinitrate in angina pectoris: comparison of duration of action and dose-response relation during acute and sustained therapy. *Am J Cardiol* 1982;**49**:411–9.

36 Rudolph W, Blasini R, Reiniger G, Brugmann U. Tolerance development during isosorbide dinitrate treatment; can it be circumvented? *Z Kardiol* 1983;**72**(suppl 3):195–8.

37 Parker JO, Farrell B, Lahey KA, Moe G. Effect of intervals between doses on the development of tolerance to isosorbide dinitrate. *N Engl J Med* 1987;**316**:1440–4.

38 Parker JO. Nitrate therapy in stable angina pectoris. *N Engl J Med* 1987;**316**:1635–42.

39 Morton WE. Occupational habituation to aliphatic nitrates and the withdrawal hazards of coronary disease and hypertension. *J Occup Med* 1977;**19**:197–200.

40 Maseri A, Chierchia S, Kaski JC. Mixed angina pectoris. *Am J Cardiol* 1985;**56**:30E–33E.

41 Joy M, Cairns AW, Sprigings D. Observations on the warm up phenomenon in angina pectoris. *Br Heart J* 1987;**58**:116–21.

42 Ignarro LJ, Lippton H, Edwards JC, *et al.* Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide; evidence for the involvement of S-nitrosothiols as active intermediates *J Pharmacol Exp Ther* 1981;**218**:739–49.

43 Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987;**327**:524–6.

44 Anonymous. EDRF. *Lancet* 1987;**ii**:137–8.

45 Shah RR, Oates NS, Idle JR, Smith RL, Lockhart JDF. Impaired oxidation of debrisoquine in patients with perhexiline neuropathy. *Br Med J* 1982;**284**:295–9.

46 Vaughan Williams EM. *Anti-arrhythmic action and the puzzle of perhexiline*. London: Academic Press, 1980.

47 Horowitz JD, Sia STB, Macdonald PS, Goble AJ, Louis WJ. Perhexiline maleate treatment for severe angina pectoris—correlations with pharmacokinetics. *Int J Cardiol* 1986;**13**:219–29.

Br Heart J 1987;58:552–5

Jubilee Editorial

Cardiology: a transatlantic view (1)

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As a cardiology trainee at the Massachusetts General Hospital I studied with Paul Dudley White. When Dr White reminisced about his medical career I heard tales of Sir Thomas Lewis and the events that led to the description of the Wolff-Parkinson-White syndrome. Dr White's experience in Britain formed the basis for the development of American cardiology. He brought back with him clinical and experimental views of the electrocardiogram, insight into the value of a careful detailed history and physical examination, and an admiration for clinical investigation that was reflected in his own subsequent work. American cardiology owes much to its British heritage and I have the sense of a personal continuum with that legacy.

During 1984–85 I was a visiting professor and consultant at the National Heart Hospital. I practised cardiology and was responsible for a firm within the hospital. I was also provided with laboratory facilities and support from the British Heart Foundation in order to carry out a laboratory project. I should like to reflect on some of my experiences with patient care and research during that period.

Many American commentators have reported on the organisation and administration of the National Health Service as an institution, comparing it with the fee for service arrangement in the United States.[1 2] I prefer to focus on the function of British cardiology rather than on its organisation. My perspective was principally limited to experiences in London teaching hospitals with an occasional visit to the provinces and to general practitioners. As a consultant, however, I dealt with physicians throughout the country and met many general practitioners participating in continuing education within the National Heart Hospital.

The patient–doctor relationship

Compared with American doctors, British physicians continue to occupy a position of much greater authority in relation to patients. My British patients rarely participated in decision-making about care, which is the practice in America. When I began to explain a procedure or treatment patients usually interrupted and suggested that they merely wanted to know what I recommended. Most of the hospital outpatient departments that I visited were characterised by a large desk that separated the patient from the physician.

I was particularly impressed by the stoicism of British patients. They rarely complained of discomfort or inconvenience. Frequently, when a procedure was complicated or unsuccessful, the patient seemed almost to apologise for the result. Several house physicians told me that they avoided American patients because Americans asked too many questions, worried about costs, and took too much time.

It was reassuring for patients to place themselves so completely in doctor's hands. A Law Lord described this as "trust." This response, however, often minimised the patient's responsibility for his or her own health. This was particularly true when changes in life style were discussed—for example, alterations in diet, cigarette smoking, or physical activity.

Many British colleagues told me that the interest of American patients in procedures and the greater development of informed consent in the United States arose out of the malpractice problem. In part this is true, particularly, for informed consent. But this view overlooks the advantages that accrue from general knowledge and understanding of health, disease prevention, and risk factor modification. Death rates from ischaemic heart disease fell by 40% in North America between 1963 and 1982. Several studies, particularly the long term follow up by Du-

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pont of all of its employees,[3] showed that until the end of 1975 the principal change was a decrease in first events—that is death, heart attack, and angina. After 1975 increased survival after a coronary event contributed to improved outcomes. Life expectancy in North America has increased. Northern Ireland, Scotland, and Wales and England now have the highest death rates from ischaemic heart disease of the Western industrialised world.[4] British physicians continue to point out possible discrepancies in arguments for the cholesterol hypothesis, to criticise efforts to control mild or moderate hypertension, and to minimise efforts at weight control while attributing the failure of the death rate to decline to a lack of cardiologists. Meanwhile Australia, New Zealand, and most of Western Europe are becoming healthier in terms of heart disease.

There seemed to be a general medical apathy about disease prevention in Britain. This is remarkable in a society that unravelled the epidemiology of cholera and the link between cigarette smoking and cancer. In a Channel 4 debate on nutrition and cardiovascular health I saw a distinguished British cardiologist argue that the plight of the country's dairy farmers should not be exacerbated by recommendations about the consumption of dairy products. I found this comment remarkable in the light of the tradition that the physician's responsibility is to the patient and not to any other party or group. What is the responsibility of British cardiology to prevention and to patient education? If the patient is to be so completely trusting is there not greater responsibility for health maintenance, counselling, and prevention? While some of the leaders of British cardiology continue to denigrate the cholesterol-diet hypothesis, vigorous efforts at prevention are lacking and death rates remain high.

Medical outcomes

There are of course great differences in the nature of services and the rate of their provision within the National Health Service compared with other health care delivery systems. I believe that American medicine tries to do too much to terminally ill patients, to the elderly, and even as part of routine care. The United States spends approximately 11·4% of its gross national product on health while Britain spends approximately 5·6%. In North America health services research is revealing many examples of over-utilisation and the rate of the rise in cost has begun to slow. Prospective payments (diagnosis related groups) have sharply shortened length of hospital stays. But in London I had difficulty in obtaining current information on health care results where under-utilisation and/or long delays in treatment were suspected. How many patients die while awaiting bypass surgery? What are the outcomes of care provided in one area where the wait for operation is twice as long as in another area? With continuing cuts to the National Health Service budget should not vigorous health services research be mandatory in order to deal rationally with public policy? Have closures of casualty departments affected emergency care mortality and morbidity? If the United States spends too much, how does one rationally decide what is too little?

A corollary to the problem arises out of the traditional role of the British consultant cardiologist who does all things. Even in large teaching hospitals some cardiologists insist upon doing all procedures upon their patients. There was a striking example of this in a report to a meeting of the British Cardiac Society that I attended. The report focused upon the indications for emergency surgical operations after angioplasty. In this study the overall surgical rate was unacceptably high by any standards. When I inquired I learned that four different cardiologists had performed the initial 66 angioplasties in the series. In view of the well documented learning curve for angioplasties it is clear that only one or two cardiologists should have performed these procedures until an acceptable experience and result had been achieved. With increasing subspecialisation in cardiology I doubt whether such practices are in the patients' best interest.

It was a great surprise to find the extent to which British cardiology has come to rely upon technology in the "American style" rather than upon excellent history taking and physical examination. As an admirer of the Paul Wood and Aubrey Leatham tradition it came as a shock to find a new breed of British cardiologists who were as dependent upon procedures as their North American cousins.

Cardiology research

Clinical research in cardiology in Britain continues to do well. In part this is because of an historical commitment to clinical cardiology and to greater ease in obtaining informed consent and patient agreement to participate in clinical studies. In North America there is a strong sense that cardiology research must have a larger component that is fundamental and cellular. Molecular biology has already had many impacts, including the production of tissue-type plasminogen activator and monoclonal antibodies, and the cloning of membrane channels. Basic science will form an increasingly important foundation of cardiology. Programmes must be developed to increase the intellectual content and stimulate advances in basic and clinical research in cardiology. I was fortunate to work at the Cardiothoracic Institute at the National Heart Hospital, which is successfully developing such a programme. But there are few other programmes of this type in Britain. The desire of cardiologists to be generalists may have inhibited this development. Basic research in cardiology requires substantial amounts of time. Cardiologists doing such research cannot maintain skills and devote the time necessary to perform catheterisations and angioplasties, or insert pacemakers. An increasing differentiation of the role of the academic cardiologist is needed.

One of the striking features of British science is the tradition that the laboratory investigator conducts all aspects of his or her research: from designing and constructing the electronic equipment to programming the computer; carrying out the experiment; and, in some circumstances, cleaning the glassware. Modern science increasingly demands specialisation, core facilities, technical support experts, and complex statistical analysis. It was not clear to me that this kind of differentiation of function and expertise is occurring in cardiology research to the extent which will be required for the 1990s.

During my year in London the budgets of the National Health Service and for research were cut considerably. University dons made some abortive protests, including denying Mrs Thatcher an honorary degree, but the relative silence of physicians was striking. Casualty departments were closed, paediatric cardiac surgery funding ran out at a main London teaching hospital, and organised British cardiology seemed to be merely an interested observer.

In a discussion about what I construed to be the relative passivity of the British medical profession, a member of parliament told me that it was attributable to two features of the profession. First he said, British physicians accept cuts in services with "a stiff upper lip." Secondly, he observed, British physicians have an authority and status that they fear will be jeopardised by challenging the general public satisfaction with the National Health Service. Indeed, several physicians told me that they did not wish to criticise the health care services for fear of "undermining public confidence" in the National Health Service. Clearly the situation is more complicated than this. The government was determined to make cuts and several physicians told me that they feared retribution if they protested too loudly. After watching the government's success in the coal strike I could understand this concern. But the profession has special responsibilities to promote arguments and to protect science and health care.

The linkage between basic and applied research

Basic science in Britain has made extraordinary contributions to science and health. The number of Nobel laureates in the molecular biology laboratories at Cambridge University is a particularly striking example. In computer software, magnetic resonance imaging, and computed axial tomography scanning, to name just a few, British scientists have been in the vanguard. Yet there is a remarkable reluctance of the basic scientist to work on applications, with industry, and, in some cases, with clinicians. Contrast Cesar Milstein's Nobel prize with the paucity of British biotechnology companies exploiting monoclonal antibodies. Some of these obstacles include the traditional distain of "trade" in Britain and the necessity to keep universities and science free of "contamination" from industry and similar venal interests. When I suggested that the "Oxford Business School" and a "Cambridge Institute of Technology" would go a long way to legitimise engineering and business for the best and the brightest of Oxbridge, several people at a London dinner party suggested that this would be the ruin of civilisation's greatest universities.

Some important moves have been made—particularly the Cambridge University Computer Laboratory which has lead to the development of several successful companies. I hope that this can lead to similar development in biomedical technology.

Patient care

During my stay I experienced the National Health Service as a user. My 15 year old daughter was struck by a motorcycle and seriously injured. After over 20 minutes an ambulance arrived. No service could be provided in the field even though she had no palpable radial and only faint brachial pulses. After being brought to the casualty department of a London teaching hospital she remained screaming on a stretcher for almost 25 minutes before her blood pressure was taken at my insistence. It was reported as 70 palpable. At this point an intravenous line was inserted and fluid administered. The consultant surgeon arrived, and directed her care expertly in the casualty department and in the operating room. Thereafter her care was excellent, despite the paucity of reliable modern volume controlled respirators in the intensive care unit. The nursing care was superb, as good or better than I have ever seen anywhere. The consultants' skills were first rate, the experience of the senior registrars was obvious, and the overall care quite satisfactory.

On balance, based on experience as a physician and as the father of a patient, I would equate patient care in the several London teaching hospitals I visited with that provided at our university-affiliated county hospitals which provide care to the indigent sick. The amount of faculty contact with patients and the role of the house staff was similar. Services for inpatients are probably more easily available in our county hospitals where all diagnostic and therapeutic needs can be met on the same site. The principal advantage of the British system is in the outpatient arena where general practitioners are available to all. In Los Angeles the indigent poor are seen in the crowded outpatients of our county hospitals. America clearly has a two-class health-care system in which the private sector consumes too many resources, probably by 25%, whereas the British private sector is relatively small. I believe the National Health Service is underfunded by about 50%. If adjustments of this order of magnitude were made by both societies, the result would be expenditures of 7·5–8% of gross national product by both. Several British physicians told me that the difference in health care expenditure reflected the relative wealth of the two societies. I find it difficult to accept this interpretation, given the percentage differences.

Attitudes and the future

Many friends and colleagues expressed their view of the United States and American cardiology—Americans are competitive, impatient, materialistic, and believe that everything that is broken should be fixed. As an anglophile I treasure many English values and institutions and wish to see their preservation. At the same time I cannot accept the notion that Britain should accept that its best days have passed. British cardiology has led the way in many areas. Individual genius and talent is present and available. But new approaches are required. More flexibility in organisation and structure, integration of basic research with clinical research, a willingness of academics to relate to clinicians and industry, and increasing specialisation of functions among academic cardiologists and scientists. More resources need to be directed toward development and exploitation of specific, highly focused areas of high-tech and bio-tech. Closer scrutiny of medical outcomes and quality of care are required and an increasing willingness to emphasise prevention.

Please do not misunderstand. I am not advocating an Americanisation of Britain—that is unrealistic and presumptuous—we have enough of our own problems. Rather we must accept that cardiology is an international discipline. British cardiology must position itself to have a major role. This will require the setting of priorities and increasing the focus of attention. This can and must be done. Part of this effort should include efforts to increase public support for more funding of research and patient care.

To all of my British colleagues, particularly my sabbatical hosts, I am deeply grateful. I only hope after these comments they will speak to me again.

References

1 Aaron HJ, Schwartz WB. *The painful prescription: rationing hospital care*. Washington, DC: The Brookings Institute, 1984.

2 Schwartz WB, Aaron HJ. Rationing hospital care—lessons from Britain. *N Engl J Med* 1984;**310**:52–6.

3 Pell S, Fayerweather WE. Trends in the incidence of myocardial infarction and in associated mortality and morbidity in a large employed population 1957–1983. *N Engl J Med* 1985;**312**:1005–11.

4 Catford JC, Ford S. On the state of public ill health: premature mortality in the United Kingdom and Europe. *Br Med J* 1984;**289**:1668–70.

Br Heart J 1987;58:556–8

Jubilee Editorial

Cardiology: a transatlantic view (2)

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"*Two nations, separated by the North Atlantic Ocean and a common language*". And more, very much more.

As a near contemporary of Aubrey Leatham at St Thomas's my participation in the British Cardiac Society was meagre, since my activities in the years 1948–51 were focused on human physiology with Henry Barcroft, FRS, supplemented by the brief but inspiring interest of Sir Henry Dale. In the course of investigations in the "new" catecholamines, I enjoyed interaction with McMichael, Pickering, Grant, Sharpey-Schafer, and, newly returned from the army, Dornhorst and De Wardener. Later Max Rosenheim encouraged a brief dalliance with the clinical aspects of phaeochromocytoma. My 36 years in the United States have been spent at the Mayo Clinic (1951–65) and at Cedars-Sinai Medical Center (UCLA School of Medicine) in Los Angeles, and communication with British cardiology has been maintained through participation in the American College of Cardiology, as its President in 1972–73, and as a member of several of its committees which ensured continuing international contacts. From that perspective and through a continued interaction with many professional friends and colleagues in the United Kingdom, I should like to comment on the most apparent differences between cardiology in the United States and the United Kingdom.

To summarise the socioeconomic background of our specialty in each of the nations: the American medical "consumer" has greater expectations and makes greater demands on the providers of medical care than the "patient" in the United Kingdom. The optimal care in the United States is probably better than that available in other countries, but the worst represents a sad level of underperformance. Access to health care in the United States is not uniform. Discipline to ensure adequate performance by physicians, including cardiologists, is negligible (in contrast with the serious efforts by surgeons and the surgical subspecialists). Health care expenditure in the United States exceed 11% of gross national product, whereas in Britain it has been frozen at 6·2% since 1981. This economic commitment is magnified by the considerably higher productivity per individual in the United States. So, taking into account the scale of investment, the British health system performs remarkably well, whereas that of the United States is disappointing.

Patient expectations and attitudes

Unlike patients in the United Kingdom, the average American patient is a "consumer" who is aware of the many interventions that are claimed to delay or moderate aging, disability, and death. The American patient will "shop around" actively and critically without necessarily accepting the recommendations of one physician. Second and even third opinions may be sought before an individual finds the opinion that accords best with, perhaps, some preconceived idea. In the United States health information is widely disseminated and broadly interpreted so that, for instance, many patients with heart disease may be better informed about the role of blood lipids in atherosclerosis than the average physician or even a reasonably well-read cardiologist. The complacent cynic might say that the concern of the American patient to receive optimal health care is well placed. But the continued search for an understanding of complex biological and clinical phenomena usually leads to an inadequate appreciation of the necessary limitations. The attitude "Why do you have to let grandma die?"

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(despite the fact she is 99) may not be discouraged by a physician whose income will be increased if the patient spends a few more days in an intensive care unit. On the contrary, in the United Kingdom effective interventions in the elderly, such as aortic valve replacement in an active 70 year old, are often inappropriately withheld because of a perceived need to husband scarce resources by categorical and arbitrary decisions. Now in my own seventh decade, I believe that attention should be given to the potential for recovery and for the continued enjoyment of life rather than social usefulness.

The health system in the United States is, in brief, a free-market enterprise. In general, physicians (and cardiologists) practise from a private office, alone or in a small group with several other specialists within or outside their own discipline. Most physicians have appointments at hospitals where they admit and treat their patients throughout a variety of illnesses—unlike the United Kingdom where the management of the patient is taken over by the hospital doctor. A trained cardiologist will see patients in his private outpatient office and also bring them to the hospital where he may conduct various specialist procedures. For example, most recently trained cardiologists believe that they are competent in diagnostic catheterisation, electrocardiography, echocardiography, coronary and critical care; and a smaller proportion claim expertise in coronary angioplasty, electrophysiology, arrhythmia management, nuclear cardiology studies, and cardiac rehabilitation. There are specialist referral systems and successful ones flourish—but no specific system is required. So the cardiological experience of an individual cardiologist may be diluted because many continue to act as general physicians treating the non-cardiac aspects of the patient.

True skills in procedures that require continued updating, experience, and a large patient volume such as coronary angiography and angioplasty, may be difficult to maintain. Specialist cardiological care is delivered in community hospitals and not at the large well-known referral centres. Many community hospitals provide all the services which are expected of a prominent university medical centre such as Stanford or a specialty clinic such as the Cleveland Clinic. The quality of diagnostic and therapeutic procedures in such community hospitals is satisfactory. It remains to be seen whether younger cardiologists will maintain sufficient skills, or whether there will be a fall out of the less competent so that with market forces only the best will continue. This "system" is clearly totally different from all but a few institutions in the United Kingdom, where a small number of specialists in cardiology are clearly defined and are in salaried posts rather than receiving a fee-for-service payment. Physicians in the United States usually continue to practise into their late 60s and even mid 70s. In an unregulated system, this has benefits and drawbacks. Most technical procedures are, however, currently performed by much younger cardiologists who continue to update their training and particularly their technical skills.

Cardiovascular manpower and training

Approximately 15 000 physicians in the United States call themselves cardiologists. Most (perhaps 80%) are certified by the sub-board in cardiovascular diseases of the American Board of Internal Medicine. Cardiovascular training in the United States is regulated to an extent unknown in the United Kingdom. Applicants for training must have completed at least two, and preferably three, years of general internal medicine and require evidence of Internal Medicine Board certification or eligibility. The cardiovascular Boards require at least two years practice in cardiology with experience of coronary care, cardiac catheterisation, and laboratory techniques. In practice, however, most training programmes last three years, and training in certain techniques, such as coronary angioplasty, may require four years. Currently, cardiologists can train in any institution with an approved programme in internal medicine. Nevertheless, most programmes are conducted in institutions with larger clinical programmes in cardiovascular disease and usually several salaried or geographically (that is, those who practice at a hospital exclusively but charge and retain private fees) full time experts. A weakness in many American programmes is the lack of experience with outpatients, as most patients consult private physicians whose income depends upon their office practice. As in general internal medicine, this deficiency is recognised by the certifying boards and there are plans to correct it.

The usual training programme in the United States requires specific "time-block" rotation through several laboratories, unlike the activities of a cardiac registrar—the equivalent in cardiology training in the United Kingdom. This means that cardiologists will be trained by several experts with special skills. Familiarity with nuclear cardiology is obligatory and physicians in training can elect to spend time obtaining certification to conduct cardiac nuclear studies. Requirements for training in cardiac catheterisation vary greatly. Most programmes require 2–4 months of "familiarisation", including training in right heart catheterisation and experience of coronary arteriography and perhaps percutaneous transluminal coronary angioplasty. Physicians who qualify and have a strong interest in cardiac catheterisation usually spend a full year in a catheterisation laboratory and become proficient in coronary arteriography. Physicians who intend to practise angioplasty train for an additional 6–12 months. Similarly, longer training periods are needed for cardiac pacing, where there is surgically supervised specialised training in techniques of implantation and electrocardiographic interpretation. Electrocardiographic departments in the United States also require expertise in dynamic (Holter) monitoring for both arrhythmias and myocardial ischaemia. These departments may be responsible for exercise testing (now often conducted in association with sections of nuclear cardiography and echocardiography). These various training programmes produce physicians with two to three years training in cardiology and modern therapeutics, including cardiac surgery, thrombolysis, and percutaneous transluminal coronary angiography.

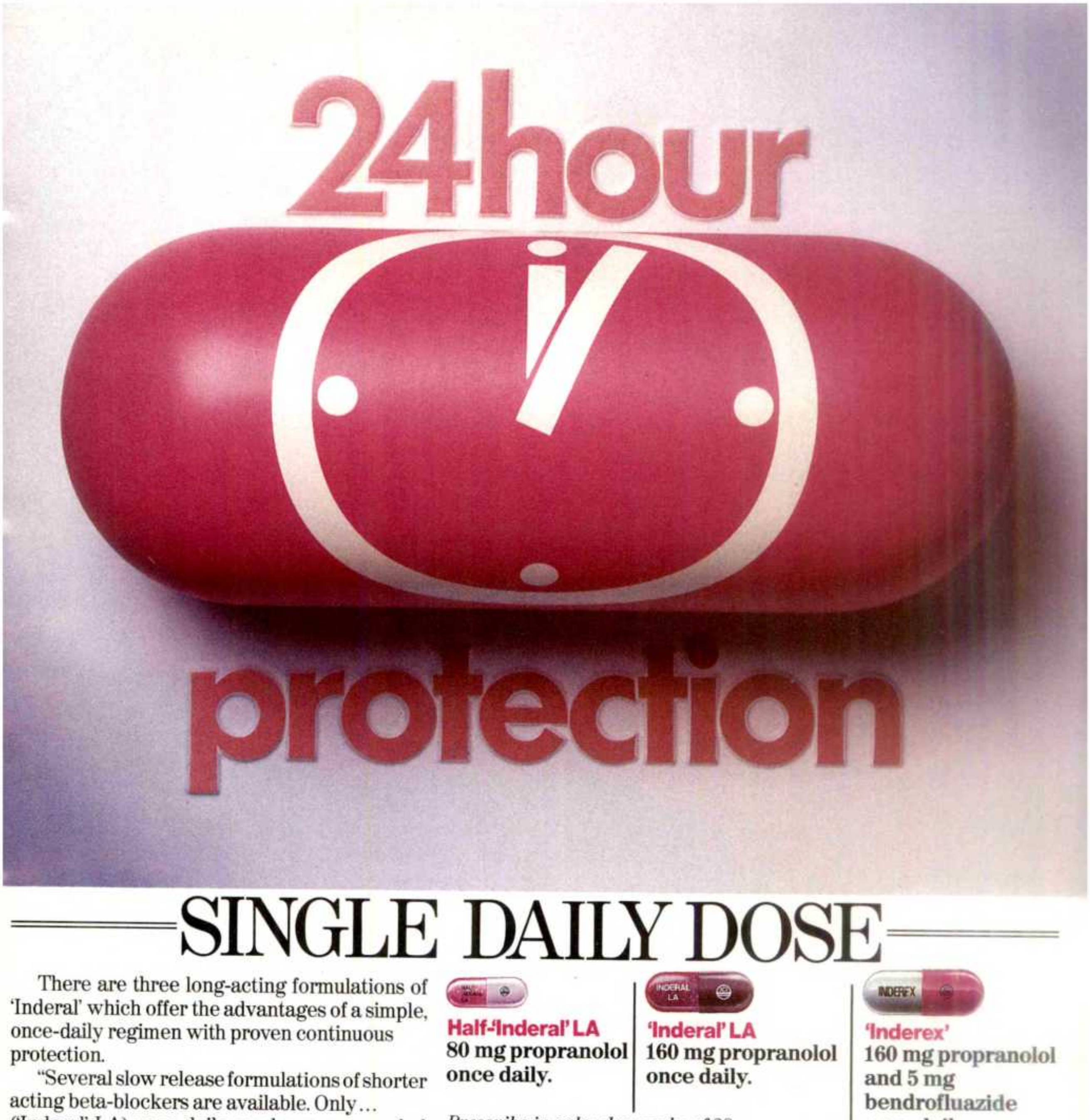
Trainees also complete a research project lasting at least six months. Although few trainees will acquire expert research skills during the project they will be able to study a topic of special interest in depth. In several programmes research is done soon after starting training in cardiology and the trainee can continue to expand his or her interest throughout the programme.

Every two years the American Boards of Internal Medicine set examinations in which most (80%) of the 1500 candidates are successful. After certification the trainees usually join an established private practice. A few remain in their training programme or at university. Not many try to establish a new private practice in cardiology. Although most are paid by private patients on a fee-for-service basis (including those who are insured or covered by Medicare), physicians are increasingly seeking salaried employment. In addition to universities and university affiliated community hospitals, leading hospitals employ full time directors and providers of radiological services on a variety of terms. In addition, many private clinics (for example Mayo, Scott-White, and Cleveland), the Veterans' Administration, and pre-paid health plans such as the Kaiser-Permanente group employ cardiologists. In several of these organisations those with extra skills are paid more.

Thus the training programmes and career structures in cardiology in the United States and the United Kingdom are different. The United States has a large number of trained cardiologists and most of them find work. There are probably several times as many cardiologists in greater Los Angeles as there are in the whole of the United Kingdom. Are they needed and do they improve cardiovascular health? I think they do. Much can be done to prolong life and improve its quality by prevention and effective and timely diagnosis and treatment of hypertensive, atherosclerotic, valvar heart disease, and arrhythmias. Is the continuing increase in cardiologists necessary to achieve these goals? Would outcomes be enhanced with *centres* for angioplasty, optimal use of cardiac pacemaking and cardiac surgery, and systematic and consistent treatment protocols? Under such circumstances could optimal services cost less? Again, the answer is probably yes. Indeed, in the United States, attempts to satisfy the administrative bureaucracy have become a fiscal nightmare. The primary overhead costs of health care (before physician, hospital, and other indirect costs) is in excess of 80 billion dollars. And many of the most needy—the poor, the immigrant, the elderly—never enter the medical care system because it is too complex and they just don't know how to.

In contrast, the National Health Service in the United Kingdom is largely understood by the citizens that it serves, although their demands on it are, comparatively speaking, small. It is probably "underproviding", but on a uniform basis. It is certainly grossly underfunded. Is American cardiology suffering from "excesses" of resources, equipment, procedures, and staff? Certainly basic and clinical research seem to be thriving. The developments of knowledge, particularly in basic science, will improve the ability of cardiologists to treat cardiovascular disease. Much of this advance is the result of the enthusiasm, vigour, and ingenuity of basic and clinical research in the United States. Every major medical journal in the United States contains new information and new insights, not only from the established university medical centres, but also from well-directed community facilities and from industrial laboratories. New ideas are often applied to treatment—many fail, but others lead to major advances in cardiovascular health care.

Yes, indeed, the differences are great. In the best of all worlds, however, the combination of the virtues and the exclusion of the vices (including bureaucratic waste and human greed) of each system will enhance the quality of life of our patients.



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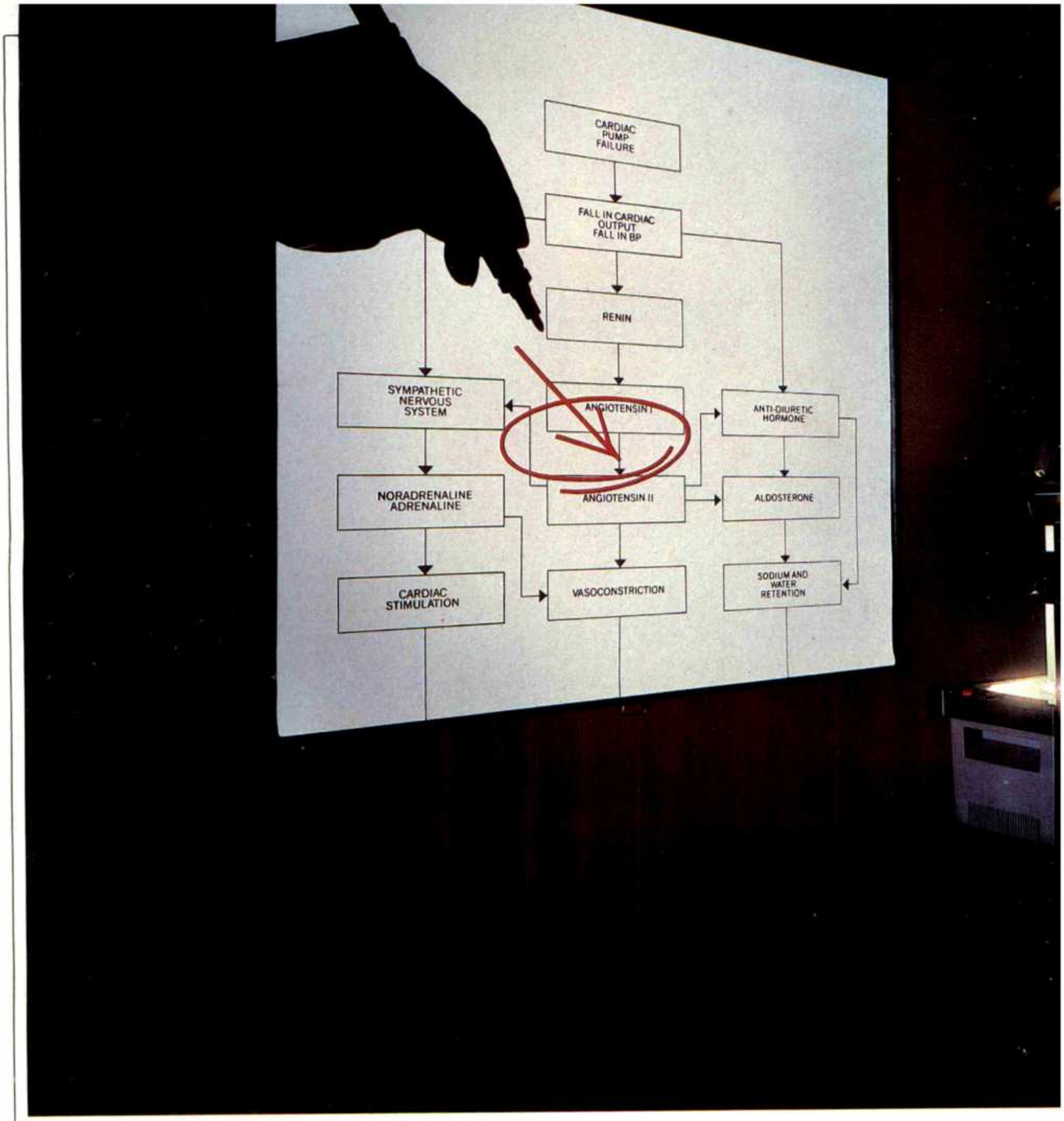

A welcome break in the vicious circle

The so-called *'vicious circle'* in heart failure results from the body's own compensator mechanisms which act to increase cardiac output and blood pressure. Unfortunately, they may also contribute to a worsening of heart failure by increasing cardiac workloa and vasoconstriction.

Central to the *'vicious circle'* is angiotensin II. While conventional therapies, in particular diuretics, relieve one or more of the symptoms of heart failure they can perpetuate the *'vicious circle'* by stimulating the production of angiotensin II In contrast 'Innovace' (enalapril maleate, MSD), by blocking the production of angiotensin II, breaks the *'vicious circle'*, resulting in reductions in aldosterone productio stimulation of the sympathetic nervous system and vasoconstriction.

Thus, as an adjunct to diuretic therapy, it is logical to use 'Innovace' to allow long-term improvement in the symptoms of moderate to severe chronic heart failure.

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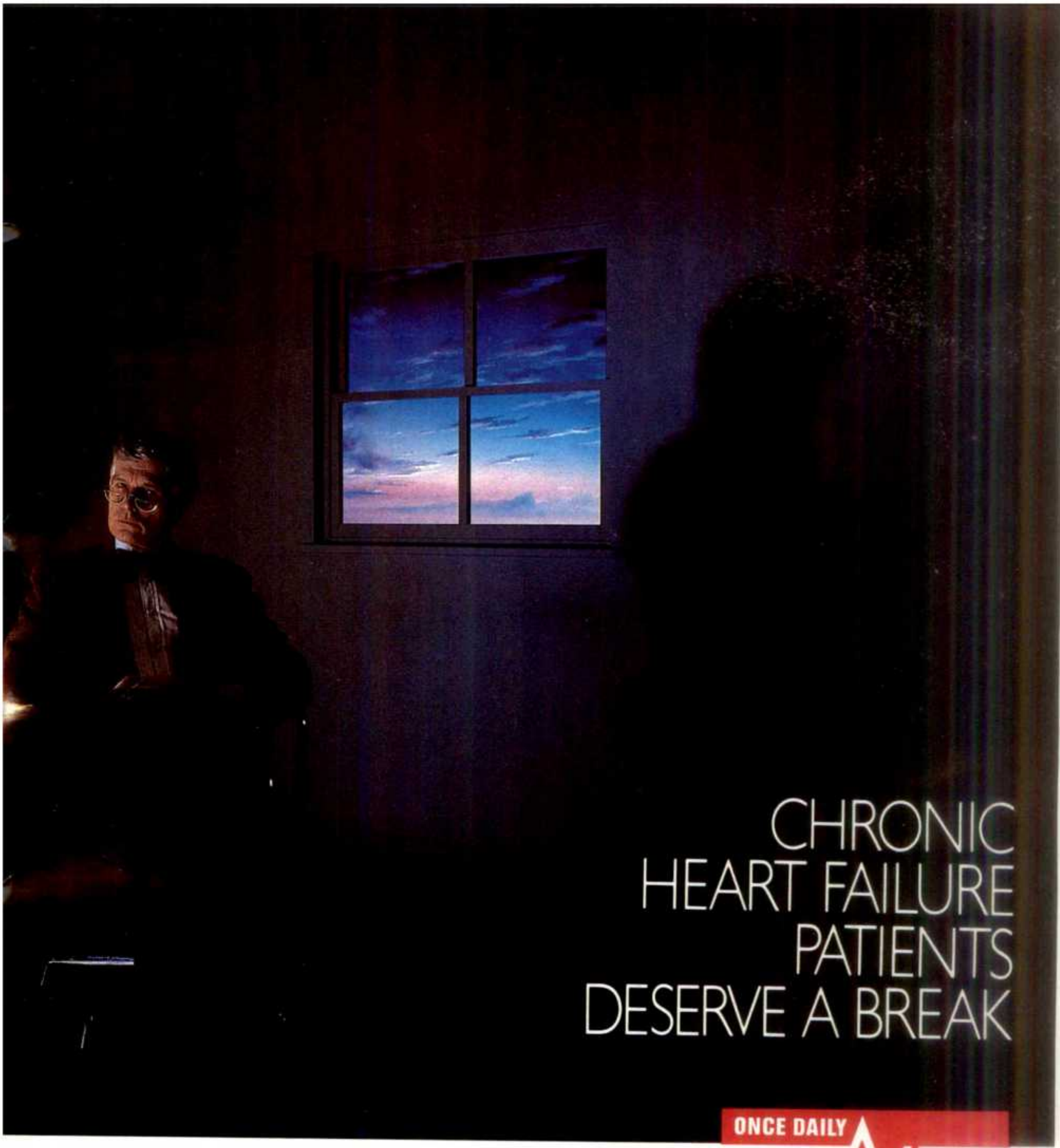

A sustained break from their symptoms

'Innovace' may provide moderate to severe heart failure patients, even those clinically stable on diuretic therapy, with significant symptomatic improvement.

This symptomatic improvement, in parameters such as decreased breathlessness and increased exercise capacity, is sustained. However, it is important to exercise care in treating heart failure patients, particularly those who are severely ill and on high doses of diuretics.

Blood pressure and renal function should be monitored closely, both before and during treatment, because hypotension and renal impairment can occur. Reducing the dose of diuretics and starting therapy in hospital under close supervision with the recommended low dose of 2.5 mg of 'Innovace' helps minimise the incidence of early hypotension and facilitates initiation of therapy. Using 'Innovace' to break the *'vicious circle'* can go a long way to offer chronic heart failure patients benefits they may have not thought possible.

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(enalapril maleate, MSD)

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Full prescribing information is available and should be consulted before prescribing.

USES
All grades of essential hypertension and renovascular hypertension where standard therapy is ineffective or inappropriate because of adverse effects.

In congestive heart failure, as adjunctive therapy with digitalis and diuretics, treatment should always be initiated in hospital.

DOSAGE
Essential and renovascular hypertension: Therapy should be initiated with 5 mg in patients under 65 years of age; 2.5 mg if older or in presence of renal impairment. The usual maintenance dose is 10–20 mg once daily; maximum 40 mg once daily. When adding to a diuretic, the starting dose of 'Innovace' is 2.5 mg with the diuretic discontinued for 2–3 days prior to 'Innovace', if possible.

Reduce beta-blocker dose gradually after starting 'Innovace'. Dose titrate to BP requirements. Dosage of other antihypertensives may need adjusting.

Congestive heart failure: Can be used as adjunctive therapy with diuretics and, where appropriate, digitalis. Initial daily dose 2.5 mg under close supervision in hospital. If possible, diuretic dose should be reduced beforehand. Monitor blood pressure closely for hypotension.

Increase dose gradually to usual maintenance dose of 10–20 mg daily.

MODE OF ACTION
Following oral administration, 'Innovace' is rapidly absorbed and hydrolysed to enalaprilat, a highly specific, long-acting, non-sulphydryl angiotensin-converting enzyme inhibitor.

CONTRA-INDICATIONS
Pregnancy: assessment for possible pregnancy required if menstrual period is missed. Hypersensitivity.

PRECAUTIONS
Assess renal function prior to therapy with 'Innovace' and during treatment where appropriate. Should not be given with aortic stenosis or outflow tract obstruction.

Symptomatic hypotension is more likely following volume depletion caused by diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting or in patients with congestive heart failure with or without renal insufficiency. Severe hypotension reported mainly in patients with severe heart failure.

Impaired renal function: Caution should be used in patients with renal impairment. Renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Renal failure has been reported, mainly in patients with severe congestive heart failure or underlying renal disease, and is usually reversible. Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying artery stenosis. 'Innovace' is dialysable.

Renovascular hypertension: 'Innovace' can be used when surgery is not indicated or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases in blood urea and creatinine, reversible upon discontinuation of therapy, have been seen.

Because it is not known whether 'Innovace' is excreted in human milk, caution required if given to nursing mothers. Has not been studied in children.

Surgery/anaesthesia: 'Innovace' may lead to hypotension requiring volume expansion.

Drug interactions: Increased antihypertensive effect when combined with methyldopa, beta-blockers, calcium antagonists, or diuretics. Adrenergic-blocking drugs should be added with caution. Concomitant propranolol may reduce bioavailability. Lithium levels may be increased.

Plasma potassium usually remains within normal limits. 'Innovace' may elevate plasma potassium levels in patients with renal failure. Potassium supplements or potassium-sparing diuretics are not usually recommended, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. If deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

SIDE EFFECTS
Severe hypotension and renal failure.

Angioneurotic oedema has occurred rarely. Discontinue 'Innovace'; condition usually resolves without treatment, but give subcutaneous adrenaline (0.5 ml 1:1,000) if airways obstruction likely.

Most frequently, dizziness, and headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, urticaria, dysgeusia, and cough.

Clinical laboratory findings: Increased blood urea and plasma creatinine, decreases in haemoglobin, platelets, white cell count, and elevation of liver enzymes have occurred in a few patients, but causal relationship not established.

Overdosage: Hypotension most likely manifestation.

BASIC NHS COST
Tablets 20 mg: calendar packs of 28 tablets, £13.10; bottles of 50 tablets, £23.40. Tablets 10 mg: calendar packs of 28 tablets, £11.03; bottles of 50 tablets, £19.69. Tablets 5 mg: calendar packs of 28 tablets, £7.86; bottles of 50 tablets, £14.03. Tablets 2.5 mg: Bottles of 50 tablets, £10.

PRODUCT LICENCE NUMBERS
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Editorial

The role of exercise testing in chronic heart failure

DAVID P LIPKIN*

From the Royal Postgraduate Medical School, Hammersmith Hospital, London

The very essence of cardiovascular practice is recognition of early heart failure and discrimination between different grades of failure (Sir Thomas Lewis, 1933).[1]

Exercise testing is often used by clinicians to diagnose and follow patients with coronary artery disease, because myocardial ischaemia during exercise produces haemodynamic and electrocardiographic changes that can be quantitatively and qualitatively defined by safe, accurate, reliable techniques. The role of exercise testing in this context is well established: its potential in the management of patients with heart failure remains to be fully exploited.[2–4] Adequacy of peripheral tissue perfusion during exercise depends upon cardiovascular performance, but exercise testing to assess overall functional capacity has been used primarily by exercise physiologists and relatively little by clinicians. Nevertheless, symptoms in chronic heart failure are manifest on exertion.

Until recently patients with heart failure were assessed solely by a questionnaire about symptoms (usually the criteria of the New York Heart Association)[5] and by clinical examination. With the appearance of new drugs it became important to document objectively the effects of treatment on cardiorespiratory fitness so that a scientific basis for treatment could be established. The limitations of the assessment of functional state by the New York Heart Association criteria are obvious. The criteria are by their nature subjective and reproducibility between observers is poor.[6] The New York Heart Association functional classification is unlikely to reflect small but clinically important changes in functional status because the categories are too broad. Because there are only four grades, it is possible that the functional class will not alter despite a clinically important change in functional status after a therapeutic intervention. Symptomatic assessment by the criteria of the Specific Activity Scale may be better than the New York Heart Association system because it is more reproducible; however, the other criticisms of the New York Heart Association assessment still apply.[6]

Why perform an exercise test?

An objective assessment should mirror the general wellbeing and exercise capacity of the patient with precision and reproducibility such that small, yet significant changes in functional state are detected in response to drug intervention, cardiac transplantation, and rehabilitation. Ideally, the assessment should provide a guide to the severity and hence prognosis of the condition. Unfortunately, there is no gold standard. General wellbeing is difficult to assess objectively, so attention has been directed to indices that can reflect changes in exercise capacity. Though a chest *x* ray is a part of the routine investigation of a patient with heart failure, two studies have demonstrated either a poor correlation or no correlation between cardiothoracic ratio and exercise capacity.[7 8] As left ventricular dysfunction is presumably the primary event that initiates the clinical syndrome of heart failure, it has been presumed that indices of left ventricular performance are related to exercise capacity. Several studies have shown that estimates of resting or peak exercise left ventricular ejection fraction or resting left ventricular end diastolic dimensions do not correlate with exercise capacity.[9–11] It is perhaps not surprising that these measurements fail to predict exercise capacity in a miscellaneous population of patients with severe heart failure. The mechanism by which these patients increase cardiac output on exercise varies with the aetiology of the heart failure.[12] Patients with idiopathic dilated cardio-

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myopathy increase stroke volume by increasing the ejection fraction and with little change in left ventricular end diastolic dimensions, whereas patients with poor left ventricular function secondary to ischaemic heart disease have larger increases in left ventricular end diastolic and end systolic dimensions with the result that there is no change in ejection fraction.

Attention has recently been directed to the importance of the right ventricle in heart failure in determining exercise capacity.[7 10] Exercise capacity appears to correlate with pulmonary vascular resistance[13] and resting right ventricular ejection fraction.[10] Pulmonary vascular resistance in heart failure does not fall, as it does in normal subjects during exercise. Since the right ventricle may not be as extensively affected as the left ventricle by the underlying pathological process, right ventricular function is predominantly afterload dependent. So it is interesting to note that only drugs that cause dilatation of the pulmonary vascular bed can significantly increase exercise capacity in controlled trials of heart failure. Other predominantly arterial vasodilators have failed to improve exercise capacity despite producing a pronounced improvement in systemic haemodynamic and left ventricular function.[14 15] It would be optimistic, however, to expect minor changes in exercise capacity to be reflected closely by changes in right ventricular function and the pulmonary circulation. Thus it is clear that if we wish to detect an improvement in exercise capacity this has to be measured directly by some form of exercise test.

Methods of exercise testing

The choice of exercise protocol has not been satisfactorily evaluated, though recent studies provide guidelines. The bicycle ergometer is probably the best method of exercising normal volunteers.[16] The technique is simple and energy output can be predicted with greater accuracy than with other forms of exercise because the mechanical efficiency is independent of body weight. A bicycle exercise test may be undesirable as a method of assessing exercise capacity in people who have never ridden a bicycle before because the motivation and stimulation of the subject are particularly important during this form of exercise. The treadmill is preferable to the bicycle for testing middle aged and elderly subjects, though some individuals find it difficult to walk on the treadmill and view the experience as frightening. The major disadvantage of treadmill exercise is that it is difficult to standardise the workload, as factors other than treadmill speed and gradient can affect the final workload achieved. The workload can be affected by the subject holding on to the rail or walking with long or short strides.

To date most studies have reported data from maximal exercise tests, that is, an incremental test which is terminated by dyspnoea or fatigue. The safety of a graded maximal exercise test has recently been established in a group of 607 stable patients from the Veterans Administration Cooperative Heart Failure Trial.[17] At least two exercise tests were performed in all patients. Arrhythmias were the end point in <1·8%. Hypotension occurred in 0·2% of baseline tests. There were no major complications in a total of 2892 exercise tests. Ventricular tachycardia was unmasked during exercise and in the immediate recovery period in only 3·2% of patients.

Exercise protocols have usually been modified to accommodate a reduced exercise capacity. This is necessary to permit patients to exercise long enough for sufficient data to be acquired for the discrimination of different grades of exercise limitation. Haemodynamic and metabolic responses to exercise may be delayed when the cardiac output is reduced; therefore it is essential when designing a multistage exercise test, to ensure that stages are sufficiently long to permit equilibium at each exercise stage. In our laboratory we use a modified Naughton protocol with exercise stages of three minutes because we have demonstrated that metabolic and respiratory gas exchanges have reached a plateau for each workload in that time.[3]

Reliance on symptomatic end points alone can be unsatisfactory as they are clearly subjective and easily affected by observer encouragement. Recent studies have suggested that coupling respiratory gas analysis with maximal exercise testing provides a more objective assessment.[2–4 18] During muscular work there is a complex interplay of diverse physiological mechanisms that ensures that oxygen delivery is commensurate with oxygen demand. The heart, lungs, and oxygen capacity of the blood participate in these adjustments. Measurement of maximal oxygen consumption during exercise is thus an index of total cardiorespiratory function and is a measure of the maximal capacity to transfer oxygen to the tissues of the body. Although exercise duration correlates significantly with oxygen consumption, the relation between the two variables is not sufficiently strong to permit accurate estimates of oxygen consumption.[3] Furthermore, repeated exercise testing in the same individual increases exercise duration (as the subject learns to walk more "efficiently" on the treadmill) without a corresponding increase in workload as shown by an increase in maximal oxygen consumption.[3 19] This is why measurement of oxygen consumption is a better measure of exercise capacity in patients with heart failure.

Many factors (genetic, age, sex, and previous level of physical activity) affect symptom limited maximum oxygen consumption in normal individuals.[16] These effects are much less important than the gross changes in symptom limited maximum oxygen consumption seen in patients with heart failure. Many studies have claimed that as a person exercises at increasing workloads maximal oxygen consumption increases to a plateau.[2 20 21] As this is the physiological limit of the aerobic capacity of the body it is an objective assessment of individual exercise capacity. It is now clear that a physiological limit to maximal oxygen is rarely reached in patients with heart failure.[3 4 22] Nevertheless, the measurement of oxygen consumption at peak exercise, so-called "maximal" oxygen consumption, is reproducible and permits categorisation of patients into subgroups according to the severity of functional impairment.[2–4 18] Thus in one study there were significant differences in maximal oxygen consumption between patients in different New York Heart Association functional classes.[3] Two other studies did not show significant differences in maximal oxygen consumption between New York Heart Association classes II and III,[2 18] but this may have related to the definition of New York Heart Association class II in the different reports.

The ideal index of exercise capacity is one that is totally independent of patient motivation and thus completely objective. In normal individuals the oxygen consumption/heart rate response to asymptomatic submaximal exercise may provide an approximate yet objective index of maximal exercise capacity.[16] Unfortunately, in patients with heart failure the heart rate response to submaximal exercise has no predictive value,[23] perhaps because in this condition the heart rate response is affected by fear and altered baroreceptor reflexes[24] and β adrenergic function.[25] In an attempt to achieve the goal of an objective assessment there has been renewed interest in the measurement of the anaerobic threshold.[2 3 26] In the early part of this century it was found that increased workloads could be achieved without any change in blood lactate concentration from the resting value.[27] As the work rate increased beyond a certain level, the blood lactate concentration increased. The carbon dioxide combining power of the blood (essentially the bicarbonate concentration) fell with an increase in blood lactate and breathing was "stimulated to expel the carbon dioxide set free" as the bicarbonate concentration in the blood diminished.[28] Hill *et al* postulated that during muscular exercise if the oxygen supply to contracting muscle became inadequate lactate production increased. The stage at which this increase occurred reflected the limits of cardiorespiratory function.[29] Thus during exercise patients with severe heart failure develop a metabolic acidosis more quickly than those with mild heart failure. Because the onset of the acidosis is presumably independent of patient motivation its detection gives an objective assessment of cardiorespiratory fitness. Wasserman and McIlroy introduced the term "anaerobic threshold" and elaborated on the concept that pulmonary gas exchange measured at the mouth could be used to detect the onset of a metabolic (lactate) acidosis.[30] The respiratory anaerobic "threshold" can be determined by several methods, the most common being a non-linear increase in minute ventilation or carbon dioxide production relative to oxygen consumption.

Recently the concept of an anaerobic threshold has been challenged for the following reasons.[31] Firstly, plasma lactate concentration is the net result of lactate production and removal. The rate of lactate production can be three times higher than during rest while blood lactate remains at resting values. Secondly, training increases lactate clearance but not lactate production. Thirdly, and arguably the most important challenge, lactate production may occur in fully oxygenated conditions with activation of fast twitch skeletal muscle fibres. Furthermore, there is debate about whether a rise in plasma lactate is linked with the ventilatory anaerobic threshold.[31] The postulated association between an increase in lactate and the ventilatory stimulus is supported by evidence from individuals who have had surgical resection of the carotid bodies.[32] These individuals have a smaller ventilatory response to exercise above the anaerobic threshold. None the less, patients with McArdle's syndrome also have a ventilatory anaerobic threshold despite an inability to produce lactate,[33] but because exercise induces pain in this disease the disproportionate increase in ventilation during exercise is likely to be caused by hyperventilation in response to pain.[34] Some investigators have found a close association between the ventilatory anaerobic threshold in patients with heart failure and the rise in blood lactate[26]; others have not.[4] The confusion has in part occurred because of the different methods of determining the anaerobic threshold and detecting where, if at all, there is a sharp rise in plasma lactate or in fact a discrete ventilatory threshold. Computerised analysis, using a curve fitting model, of the oxygen consumption/carbon dioxide production relation during exercise appears to avoid the problem of defining a discrete ventilatory threshold. This promising new technique provides a refinement to the concept of anaerobic threshold and, it is hoped, greater objectivity.[35]

The anaerobic "threshold" is in part determined by a lactate acidosis during exercise, but other factors may be important. Measurement of the ventilatory anaerobic threshold has two potential uses. First, it can be used as a general index of patient motivation. Failure to achieve the ventilatory anaerobic threshold suggests poor patient motivation. Secondly, changes in maximum oxygen consumption in the absence of change in the anaerobic threshold suggest an alteration in patient motivation rather than a change in functional capacity. Assessment of maximum oxygen consumption alone can be misleading, but linked with knowledge of the anaerobic threshold these measurements provide an objective and accurate means of classifying and following patients with heart failure.[2]

The equipment required to measure respiratory gas exchange is expensive and some patients find it difficult to exercise on a treadmill. High workloads are not typical of activities performed by these patients in daily life. In patients with moderate to severe disability it may be more reasonable to measure exercise capacity at constant submaximal workloads, for example 60–70% of symptom limited maximal oxygen consumption. Unfortunately these tests may be difficult to perform as the duration of exercise may be considerable and boredom may be a limiting factor. Various groups have used a 2, 6, and 12 minute walking test to monitor exercise capacity in normal subjects and patients with obstructive lung disease. Recently, a test which simply measures the distance walked in six minutes has been used to assess patients with heart failure.[36] Patients preferred the six minute walking test to the treadmill, finding it easier and more closely related to their daily level of physical activity. There were wide ranges of six minute distances walked among those patients with a very low maximal oxygen consumption. Some of these individuals may have been poor treadmill performers who produced a better account of their abilities during the walking test. Conversely, there was little variation in the six minute distance in normal subjects and in patients with mild heart failure despite noticeable differences in their maximal exercise capacities. In those with mild heart failure the maximal rather than the submaximal test may be a more suitable method of assessing exercise capacity, as exercise is performed at workloads sufficient to cause symptoms.[36]

To summarise, the choice of exercise protocol used to assess patients with heart failure is partly determined by available facilities. Maximal exercise testing is conventional, and should if possible be linked with respiratory gas analysis. Submaximal exercise tests may be more appropriate in patients with severe failure, and may gain popularity especially in centres that do not have access to gas analysis equipment.

Symptoms limiting exercise tolerance

The symptoms limiting exercise in patients with heart failure are difficult to evaluate.[37] Exercise testing linked with analysis of respiratory gas exchange and haemodynamic assessment has permitted insight into the problem. Classic teaching suggests that breathlessness in patients with heart disease is caused by pulmonary venous hypertension and fatigue by an inadequate increase in cardiac output on exercise. Though this may be the case in acute heart failure, the situation is less clear once chronic heart failure is established. The feeling of breathlessness appears to be independent of changes in left atrial pressure (as estimated from the pulmonary capillary wedge pressure). There is no correlation between the wedge pressure at rest or during maximal exercise and maximal oxygen consumption reached at the end of symptom limited exercise.[8 9 38 39] The symptom which terminates exercise depends on the type of exercise performed rather than peak wedge pressure. Slow exercise is usually terminated by fatigue whereas rapid exercise is terminated by dyspnoea despite a similar peak pulmonary capillary wedge pressure at the end of each form of exercise.[39] Furthermore, when submaximal and maximal exercise tests are compared, both forms of exercise are terminated at identical ventilatory levels and peak exercise pulmonary capillary wedge pressures.[40] If the primary stimulus to excessive ventilation during exercise was an acute increase in pulmonary venous pressure then the increase in ventilation would be greater during more prolonged submaximal exercise. In addition, long term drug studies have shown that an improvement in exercise capacity is often, but not invariably, associated with an improvement in haemodynamic function and a fall in pulmonary capillary wedge pressure during exercise. Short term vasodilators and inotropic agents almost always improve the haemodynamic indices and lower the pulmonary capillary wedge pressure, but usually do not increase exercise capacity in the long term.[14] An alternative explanation relates the many complex metabolic changes that occur during exercise.[39] Blood flow through skeletal muscle is reduced in patients with heart failure.[41] A lactic acidosis develops during rapid forms of exercise and may stimulate peripheral chemoreceptors which contribute to the hyperventilatory response and feeling of breathlessness.[39]

The mechanisms of fatigue in heart failure are elusive. Fatigue is associated with inadequate oxygen supply to skeletal muscle. During maximal exercise testing, the oxygen content of blood in the femoral vein is negligible.[42] Wilson *et al* showed that patients with chronic heart failure became fatigued when underperfusion of skeletal muscle reached a critical level; they concluded that fatigue in patients with heart failure was caused by impaired nutrient flow to skeletal muscle.[43] The mechanisms may be intracellular acidosis, caused by accumulation of lactate, or depletion of phosphocreatine.[43] Alternatively, there may be persistent changes in skeletal muscle function in chronic heart failure caused by deconditioning which also contribute to exercise limitation in these patients.[44] After cardiac transplantation, despite virtually immediate restoration of a normal resting cardiac output, the expected increase in exercise capacity is delayed over several months.[45] This response may relate to a gradual reduction in those factors that limit skeletal muscle blood flow or to a gradual improvement in the function of skeletal muscle.[44] What these research findings show, then, is that the limitation of exercise and the feelings of breathlessness or fatigue in patients with chronic heart failure have multifactorial mechanisms. Their symptoms should not be related solely to an altered haemodynamic response to exercise. The symptom that limits an individual patient will depend on the different mechanisms influencing neural and metabolic signals from exercising muscle and the response of more central receptors.

Rehabilitation in heart failure

Surprisingly, the effect of regular exercise testing per se on exercise capacity has not been extensively studied. There are only two published reports.[46 47] Regular exercise (30 minutes, three times per week at 60–70% of maximal oxygen consumption for 15 weeks) improves cardiac output and reduces pulmonary capillary wedge pressure at submaximal exercise workloads and increases symptom limited maximal oxygen consumption by 25%.[47] It has been suggested that the improvement in maximal exercise capacity is related to an improvement in skeletal muscle blood flow,[47] yet the same group also showed that short term treatment with dobutamine increases blood flow to skeletal muscle during submaximal exercise but does not augment maximal oxygen consumption.[48] Regular training probably improves exercise capacity partly because of the cardiovascular training effect, but also perhaps because of a direct peripheral effect, presumably on skeletal muscle function. Further longitudinal studies are required to evaluate the effect of treatment and rehabilitation on the performance of skeletal muscle in heart failure.

Prognosis in heart failure

Prolonged survival remains the major goal of treatment. From the time of initial diagnosis of heart failure, overall mortality exceeds 50% within five years.[49] In patients who remain symptomatic despite treatment with diuretics, the mortality rate is approximately 75% over three years.[50 51] Until recently there was no evidence that treatment, with the presumed exception of cardiac transplantation, altered this terrible prognosis.[50 52] The detection of any possible positive association between survival and treatment has been delayed by a tendency to perform small drug studies with an inadequate duration of follow up. Combined data from the trials of angiotensin converting enzyme inhibitors appear promising and the published results of large trials are awaited.[50] The results of a large trial of the effects of enalapril in heart failure have now been published. Enalapril reduced mortality at six months and one year by 40% and 31% respectively when compared with placebo.[53] The data from the Veterans Administration Cooperative Heart Failure Trial study demonstrate a 28% reduction in long term mortality with hydralazine and isosorbide dinitrate compared with placebo.[52] To alter significantly the course of the disease, it is essential to recognise indicators of outcome. Data relating to haemodynamic function are conflicting.[54 55] Though the left ventricular ejection fraction does not correlate with exercise capacity, it is an important predictor of survival.[56] The importance of non-sustained ventricular tachycardia is less clear. Though the presence of ventricular tachycardia correlates with mortality it is not clear whether it predicts sudden death.[57] Concentrations of plasma noradrenaline[58] and serum sodium[59] determined from a single blood sample may provide a guide to prognosis in heart failure. The cynic might say that the obvious conclusion from all these studies is that the sicker the patients, the quicker they will die.

Most of the indices of prognosis are not independent predictors of survival. Because the known predictors of survival do not relate to exercise capacity, it is pertinent to assess the prognostic significance of exercise testing. It is clear that the more severe the functional disability at the time of presentation with heart failure, the worse the prognosis.[55 56] As previously stated, however, New York Heart Association assessment is unreliable. Exercise capacity as assessed by maximal oxygen consumption may provide a simple non-invasive prognostic index. But in a relatively small study maximal oxygen consumption was found to be reduced to the same extent in survivors and non-survivors.[60] Other studies show a relation between maximal oxygen consumption and prognosis. One investigation divided patients into two groups: group 1 had maximal oxygen consumption of <10 ml/kg/min and group 2 had maximal oxygen consumption >10 ml/kg/min. The one year mortality for group 1 and group 2 was 21% and 77% respectively ($p < 0{\cdot}001$).[61] Two larger studies, of 136 and 637 patients respectively,[62 63] showed that maximal oxygen consumption was a highly independent predictor of survival ($p < 0{\cdot}005$), which in turn was a better predictor than exercise duration or left ventricular ejection fraction. Thus quantitative exercise tolerance also provides an important guide to prognosis in heart failure.

Conclusions

The clinical syndrome of heart failure is disabling and has a high mortality with a prognosis that is worse than many cancers. Exercise testing is a useful tool for assessing the severity of the disease. Measurement of functional capacity based on respiratory gas exchange during exercise permits greater understanding of the pathophysiology of symptoms and provides an objective method of assessing responses to pharmacological and rehabilitative interventions. The major aim of treatment in this condition is to reduce mortality. It is unlikely that we can have a major impact on survival once heart failure is established. Surely it would be more rewarding to develop strategies aimed at early intervention? Perhaps an ability to perceive early deterioration will permit a more logical approach to treatment and optimise the timing of cardiac transplantation. A scientific approach to understanding the pathophysiology and treatment of heart failure can no longer rely on subjective or crude measurements of left ventricular function.

References

1 Lewis T. *Diseases of the heart*. New York: Macmillan, 1933:1.

2 Weber KT, Kinasewitz GT, Janicki JS, Fisherman AP. Oxygen utilisation and ventilation during exercise in patients with chronic heart failure. *Circulation* 1982;**65**:1213–23.

3 Lipkin DP, Perrins J, Poole-Wilson PA. Respiratory gas exchange in the assessment of patients with impaired ventricular function. *Br Heart J* 1985; **54**:321–8.

4 Wilson JR, Fink LI, Ferraro N, Dunkman WB, Jones RA. Use of maximal bicycle exercise testing with respiratory gas analysis to assess exercise performance in patients with congestive heart failure secondary to coronary artery disease or to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1986; **58**:601–6.

5 The Criteria Committee of the New York Heart Association. *Nomenclature and criteria for diagnosis*. 6th ed. Boston: Little Brown, 1964.

6 Goldman L, Hasmoto B, Cook F, Lascalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class. *Circulation* 1981;**64**:1227–34.

7 Engler R, Ray R, Higgins CB, *et al*. Clinical assessment and follow up of functional capacity in patients with chronic congestive cardiomyopathy. *Am J Cardiol* 1982;49:1832–7.

8 Francis GS, Goldsmith SR, Cohn JN. Relationship of exercise capacity to resting left ventricular performance and basal plasma norepinephrine levels in patients with congestive heart failure. *Am Heart J* 1982;**104**:725–31.

9 Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *Am J Cardiol* 1981;47:33–9.

10 Baker BJ, Wilen MM, Boyd CM, Dinh H, Franciosa JA. Relation of right ventricular ejection fraction to exercise capacity in chronic left ventricular failure. *Am J Cardiol* 1984;**54**:596–9.

11 Higginbotham MB, Morris KG, Conn EH, Coleman RE, Cobb FR. Determinates of variable exercise performance among patients with severe left ventricular dysfunction. *Am J Cardiol* 1983;**51**:52–60.

12 Shen WF, Roubin GS, Hirasawa K, *et al*. Left ventricular volume and ejection fraction response to exercise in chronic heart failure: differences between dilated cardiomyopathy and previous myocardial infarction. *Am J Cardiol* 1985;**55**:1027–31.

13 Franciosa JA, Baker BJ, Seth L. Pulmonary versus systemic haemodynamics in determining exercise capacity of patients with chronic left ventricular failure. *Am Heart J* 1985;**110**:807–13.

14 Lipkin DP, Poole-Wilson PA. Treatment of chronic heart failure: a review of recent drug trials. *Br Med J* 1985;**291**:993–6.

15 Franciosa JA, Dunkman WB, Leddy CL. Haemodynamic effects of vasodilators and long-term response in heart failure. *J Am Coll Cardiol* 1984;**3**:1521–30.

16 Astrand PO, Rodahl R. *Textbook of work physiology—physiological basis of exercise*. New York: McGraw-Hill, 1977:331–61.

17 Tristani F, Archibald D, Hughes CV, Sheldahl L, Fletcher R, Cohn J. Safety of graded exercise testing in congestive heart failure (V-HeFT) [Abstract]. *Circulation* 1986;74(suppl II):395A.

18 Franciosa JA. Exercise testing in chronic congestive heart failure. *Am J Cardiol* 1984;**53**:1447–50.

19 Froelicher VF. Exercise testing and training: clinical applications. *J Am Coll Cardiol* 1983;**1**:114–25.

20 Taylor HL, Buskirk E, Henschel A. Maximal oxygen intake as an objective measure of cardiorespiratory performance. *J Appl Physiol* 1955;**8**:73–80.

21 Pollock ML. The quantification of endurance training

programme. In: Wilmore JH, ed. *Exercise and sports science review.* Vol. 1. New York: Academic Press, 1973:155.

22 Roberts JM, Sullivan M, Froelicher VF, Gentar F, Myers J. Predicting oxygen uptake from treadmill testing in normal subjects and coronary artery disease patients. *Am Heart J* 1984;**108**:1454–60.

23 Lipkin DP, Bayliss J, Poole-Wilson PA. The use of submaximal exercise test to predict maximal exercise capacity. *Eur Heart J* 1985;**6**:829–33.

24 Cody RJ, Franklin KW, Kluger J, Laragh JH. Mechanisms governing the postural response and baroreceptor abnormalities in chronic congestive heart failure: effects of acute and long term enzyme inhibition. *Circulation* 1982;**66**:135–42.

25 Bristow MR, Ginsberg R, Minobe W, *et al.* Decreased catecholamine sensitivity and beta-adrenoreceptor density in failing human hearts. *N Engl J Med* 1982;**307**:205–11.

26 Matsumura N, Nishijima H, Kojima S, Hashimoto F, Minami M, Yasuda H. Determination of anaerobic threshold of assessment of functional state in patients with chronic heart failure. *Circulation* 1983; **68**:360–7.

27 Christiansen J, Douglas CG, Haldane JS. The absorption and dissociation of carbon dioxide by human blood. *J Physiol (Lond)* 1914;**48**:244–8.

28 Douglas CG. Coordination of the respiration and circulation with variations in body activity. *Lancet* 1927;**213**:213–8.

29 Hill AV, Long CNH, Lupton H. Muscular exercise lactic acid and the supply and utilisation of oxygen. Part VI—the oxygen debt at the end of exercise. *Proc R Soc Lond [Biol]* 1925;**97**:127–37.

30 Wasserman K, McIlroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. *Am J Cardiol* 1964;**14**:844–52.

31 Brooks GA. Anaerobic threshold: review of concepts and directions for future research. *Med Sci Sports Exerc* 1985;**17**(part I):22–31.

32 Wasserman K, Whipp BJ, Royal SN, Cleary MG. Effect of carotid body resection on ventilatory and base control during exercise. *J Appl Physiol* 1975;**39**:354–8.

33 Hagberg JM, Coyle EF, Carroll JE, Miller JM, Martin WH, Brooke MH. Exercise hyperventilation in patients with McArdle's disease. *J Appl Physiol* 1982;**52**:991–4.

34 Whipp BJ. Exercise hyperventilation in patients with McArdle's disease [Letter]. *J Appl Physiol* 1983;**55**:1638.

35 Buller N, Poole-Wilson PA. Extrapolated maximal oxygen consumption—a new method for the objective analysis of respiratory gas exchange during exercise. *Br Heart J* 1988 (in press).

36 Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walking test for worsening exercise capacity in patients with chronic heart failure. *Br Med J* 1986;**292**:653–5.

37 Lipkin DP, Poole-Wilson PA. Symptoms limiting exercise in chronic heart failure. *Br Med J* 1986; **292**:1030–1.

38 Franciosa JA, Leddy CL, Wilen M, Schwartz DE. Relation between haemodynamic and ventilatory responses in determining exercise capacity in severe heart failure. *Am J Cardiol* 1984;**53**:127–34.

39 Lipkin DP, Canepa-Anson R, Stephens MR, Poole-Wilson PA. Factors determining symptoms in chronic heart failure: comparison of fast and slow exercise tests. *Br Heart J* 1986;**55**:439–45.

40 Wilson JR, Ferraro N. Exercise intolerance in patients with chronic heart failure: relation to oxygen transport and ventilatory abnormalities. *Am J Cardiol* 1983;**51**:1358–63.

41 Wilson JR, Martin JL, Schwartz D, Ferraro N. Exercise intolerance in patients with chronic heart failure: role of impaired skeletal muscle nutritive flow. *Circulation* 1984;**69**:1079–87.

42 Donald KW, Wormold PN, Taylor SH, Bishop JM. Changes in the oxygen content of femoral venous blood and leg based flow during leg exercise in relation to the cardiac output response. *Clin Sci* 1957;**16**:567–91.

43 Wilson JR, Fink L, Maris J, *et al.* Evaluation of energy metabolism in skeletal muscle of patients with heart failure with gated phosphorus-31 nuclear magnetic resonance. *Circulation* 1985;**71**:57–62.

44 Lipkin DP, Jones DA, Round JM, Poole-Wilson PA. Maximal force, fibre type, and enzymatic activity in quadriceps of patients with severe heart failure: a mechanism for reduced exercise capacity [Abstract]. *Br Heart J* 1985;**54**:622.

45 Astrom H. Exercise testing in patients with heart disease. *Acta Pharmacol Toxicol (Copenh)* 1986; **59**(suppl 6):65–70.

46 Conn EH, Williams RS, Wallace AC Exercise response before and after physical conditioning in patients with severely depressed left ventricular function. *Am J Cardiol* 1982;**49**:296–300.

47 Maskin CS, Reddy HK, Gulanick M, Perez L. Exercise training in chronic heart failure: improvements in cardiac performance and maximal oxygen uptake [Abstract]. *Circulation* 1986;**74**(suppl II):310A.

48 Reddy HK, Weber KT, Maskin CS. Improvement in submaximal exercise performance with dobutamine therapy in patients with chronic heart failure. *Circulation* 1986;**74**(II):509A.

49 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. *N Engl J Med* 1971;**285**:1441–6.

50 Furberg C, Yusef S, Thorn TJ. Potential for altering the natural history of congestive heart failure: need for large clinical trials. *Am J Cardiol* 1985;**55**: 45A–7A.

51 Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983;**51**:831–6.

52 Cohn JN, Archibald DG, Ziesche S, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;**314**:1547–52.

53 The CONSENSUS Trial Study Group Effects of enalapril on mortality in severe congestive heart failure.

N Engl J Med 1987;316:1429–35.

54 Kannel WB, Savage D, Castelli WP. Cardiac failure in the Framingham Study: twenty year follow up. In: Braunwald E, ed. *Congestive heart failure: current research and clinical applications*. New York: Grune and Stratton, 1982:15.

55 Wilson JR, Schwartz JS, Sutton MS, *et al.* Prognosis in severe heart failure. Relation to haemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;2:403–10.

56 Califf RM, Bounous P, Harell FE, *et al.* The prognosis in the presence of coronary artery disease. In: Braunwald E, ed. *Congestive heart failure: current research and clinical applications*. New York: Grune and Stratton, 1982:31–40.

57 Francis GS. Development of arrhythmias in the patient with congestive heart failure: pathophysiology, prevalence and prognosis. *Am J Cardiol* 1966;57:3B–7B.

58 Cohn JN, Levine TB, Olivari MT, *et al.* Plasma norepinephrine as a guide to prognosis in patients with chronic heart failure. *N Engl J Med* 1984; 311:819–23.

59 Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting enzyme inhibition in patients with severe chronic heart failure. *Circulation* 1986;73:257–67.

60 Franciosa JA, Wilen MM, Baker BJ. Functional capacity and longterm survival in chronic left ventricular failure [Abstract]. *Circulation* 1983;68(suppl III):149A.

61 Szlachaic J, Massie BM, Kramer BL, Topic N, Tuban J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. *Am J Cardial* 1985;55:1037–42.

62 Cohn J, Rector T, Olivari MT, Levine TB, Francis GS. Plasma norepinephrine, ejection fraction and maximal oxygen consumption as prognostic variables in congestive heart failure. *Circulation* 1985; 72(III):285A.

63 Cohn JN, Ziesche S, Archibald DG. Quantitative exercise tolerance as a predictor of mortality in congestive heart failure: the V-HeFT study [Abstract]. *Circulation* 1986;74(suppl II):447A.

Br Heart J 1987;58:567–71

Predictors of sudden death up to 18 years after a first attack of unstable angina or myocardial infarction

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SUMMARY Factors related to the occurrence of sudden death were examined in 551 men aged <60 years who survived a first attack of unstable angina or myocardial infarction by at least 28 days. There were 301 deaths over an average follow up period of 9·4 years and 138 (46%) of these were sudden. Life table techniques permitted the estimation of mortality up to 18 years after the index event. The proportion of sudden deaths showed a decrease with length of follow up. In those who were non-smokers and in those aged <45 years on admission sudden deaths in the first two years were very common (80% (95% confidence interval: 69%–91%) and 79% (95% confidence interval: 68%–90%) respectively). The proportion of sudden deaths in the remaining 16 years of follow up was related inversely to age at initial attack. After the first two years of follow up sudden death rates were similar in those who continued to smoke and those who stopped smoking, although those who continued to smoke had a significantly higher overall mortality.

The risk of sudden death should be borne in mind when planning the investigation and rehabilitation of young and non-smoking subjects presenting with a first coronary event.

In survivors of an acute coronary event there is a high risk of sudden death particularly during the first year after hospital discharge.[1-3] The purpose of this investigation was to examine patterns of sudden death up to 18 years after a first coronary event and to identify factors related to this mode of death.

Patients and methods

Between 1 January 1965 and 31 December 1975, 555 consecutive male patients aged <60 years who survived a first attack of unstable angina or myocardial infarction by 28 days were entered into a long term follow up study (the St Vincent's Heart Study). One hundred and two (18·4%) had confirmed unstable angina. The remainder had a myocardial infarction.

The methods of study have been described elsewhere.[4] Diagnosis of myocardial infarction was based on a history of cardiac pain, fresh Q waves in the electrocardiogram, and/or a twofold or greater increase in the activity of cardiac enzymes (creatine kinase, lactic dehydrogenase, and aspartate transaminase). Unstable angina was diagnosed in patients with cardiac pain, serial ST and T wave changes, no abnormal Q waves, and no enzymatic evidence of recent myocardial necrosis.

A full risk factor profile for each patient was recorded at entry to the study and included information on age, pre-existing angina, hypertensive state, and cigarette smoking habits. Only patients with angina of effort for at least three months before entry were classified as having angina before the event. For four patients this information was missing and they were excluded. This left 551 for analysis. Patients with at least one of the following criteria were deemed to have hypertension: average diastolic pressure on fourth day after admission of >90 mm Hg; history of antihypertensive drug treatment before admission; diastolic pressure >100 mm Hg at subsequent outpatient visits during the first three months after discharge; known hypertension requiring treatment; the presence of at least two of the following: (*a*) past history of hypertension; (*b*) electrocardiographic evidence of left ventricular hypertrophy, or (*c*) hypertensive retinopathy. For the purposes of this analysis all other patients were classified as normotensive.

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Those smoking ≥5 cigarettes daily during the three months before the initial attack were classified as current smokers; those who had already ceased smoking for at least three months or were smoking <5 cigarettes a day were classified as ex-smokers, and those who never smoked cigarettes were classified as non-smokers. Primary pipe and cigar smokers were classified as non-smokers.

Each patient was seen annually at a rehabilitation and secondary prevention follow up clinic. A change in smoking habit at the first follow up was examined as a variable in this report. Initial current smokers who survived two years after the index event were classified on this basis as stopped smokers if they had ceased for at least three months at the time of the examination. We found a high degree of veracity in the stated smoking habits of a sample of these patients.[5]

Subjects were followed up to the end of 1984. Cause and mode of death were derived from hospital records, necropsy reports, death certificates, and through contact with the family physician and patients' relatives. Sudden death was defined as instantaneous death, death within one hour of the onset of symptoms, or unwitnessed death. Three hundred and one patients had died by the end of 1984. All but eight (3·2%) of the survivors were known to be alive in 1983 or 1984. The average length of follow up to death or last contact was 9·4 years.

All patients were managed conservatively with particular and repeated emphasis on risk factor modification. β blockers were used to control hypertension or in the management of severe angina of effort to facilitate an exercise program. β blockers were discontinued when exercise capacity returned to a satisfactory level. Otherwise they were not routinely used during follow up.

STATISTICAL ANALYSIS

We used the Kaplan-Meier life table[6] to estimate mortality up to 18 years after the presenting event. Eighteen patients were alive at this point. Because the numbers were small, estimates of mortality beyond 18 years were considered unreliable and are not considered in this report.

Cox's proportional hazards regression model[7] as implemented in the SAS computer package[8] was used to examine the independent effects on mortality of the factors mentioned above: age (<45; 45–49; 50–54; 55–59), severity of attack (unstable agina or myocardial infarction), angina before the coronary event, hypertension, and smoking status. These factors were entered as binary or dummy variables and were chosen because of their known influence on short or long term mortality from previous analyses.

Cause specific mortality (also taken to refer to mode specific mortality) analysis was performed with the particular cause as an end point and treating all other deaths as censored data. This allowed estimation of the "net" mortality[9]—that is the mortality from a particular cause if all other causes of death were eliminated. These net mortalities were then adjusted to give the actual cause specific mortality which is presented in the report. An appendix giving the adjustment procedure and the derivation of the variance estimates is available from the authors.

To evaluate differences between early and late mortality, and to allow for differing effects of the factors studied, separate analyses were performed for mortality in the first two years and for the subsequent 16 years of follow up. In the former case all two year survivors were treated as censored at two years and for the next sixteen years the analysis was confined to two year survivors only. Results are expressed in terms of an average annual mortality (total or cause specific) in the early or late follow up periods, which permits direct comparison between the periods. Confidence intervals are based on an approximate variance estimate.

Results

Table 1 shows the distribution of the patient characteristics that were examined for all 551 patients included in the study and for the 500 two year survivors. At two years those who were cigarette smokers at the time of their attack were further categorised into those who had stopped and those who had continued. There were 51 deaths in the first

Table 1 *Characteristics at entry to study of all patients and those surviving two years*

	All patients *No (%)*	*Two-year survivors* *No (%)*
Age:		
<45	97 (17·6)	88 (17·6)
45–49	129 (23·4)	121 (24·2)
50–54	150 (27·2)	136 (27·2)
≥55	175 (31·8)	155 (31·0)
Severity of initial attack		
Unstable angina	102 (18·5)	93 (18·6)
Myocardial infarction	449 (81·5)	407 (81·4)
Angina preceding the episode.		
Absent	405 (73·5)	375 (75·0)
Present	146 (26·5)	125 (25·0)
Hypertension:		
Absent	471 (85·5)	432 (86·4)
Present	80 (14·5)	68 (13·6)
Cigarette smoking:		
Non	49 (8·9)	43 (8·6)
Ex	96 (17·4)	84 (16·8)
Current	406 (73·7)	233 (46·6) (stopped) 140 (28·0) (continued)
Total	551 (100·0)	500 (100·0)

two years and 250 therafter. One hundred and thirty eight (45·8%) were sudden and 119 (39·5%) were attributed to other vascular causes including myocardial infarction. Table 2 shows the cumulative total, sudden death, and vascular and non-vascular mortality at selected times from study entry, based on the Kaplan-Meier life table. The proportion of sudden deaths since the index coronary event decreased with length of follow up and deaths from non-vascular causes became increasingly more important.

Table 3 shows the average annual mortality and percentage of sudden deaths separately for the two year period after the initial event and for the remaining sixteen years of follow up. The all-cause mortality increased with length of follow up (p < 0·05) while the sudden death rate showed only a marginal and non-significant increase. As a consequence the proportion of sudden deaths was lower in the later follow up period.

Table 4 shows the effect of age at study entry on subsequent mortality. In general, sudden death rates tended to increase with age. Exceptionally, in the first two years of follow up, however, those aged <45 years had the highest annual mortality from sudden deaths (3·8%) and a very high proportion of sudden deaths (79%). After two years the proportion of sudden deaths decreased with increasing age from 63% in the under 45s to 38% in those over 55.

Hypertension and the existence of angina before the index event were independently associated with increased sudden death rates—significantly so in the last 16 years of follow up. These factors also increased total mortality to the same extent and thus did not influence the proportion of sudden deaths. The effect of the severity of the initial attack (unstable angina versus myocardial infarction) on mortality was confined to the first two years of follow up. Sudden death rates and total mortality in this period were higher in those who had a myocardial infarction initially.

Based on the ordered category of non-smokers, ex-smokers, and current smokers at study entry the amount of smoking was associated with an increase in mortality from non-sudden causes and a decrease in mortality from sudden death over the first two years (table 5). Consequently the proportion of sudden deaths decreased from a high of 80% in non-smokers to a low of 50% in those smoking at the time of the initial event (p < 0·05). Over the last 16 years of follow up, however, those who had ever smoked cigarettes (initial ex-smokers and current smokers who either ceased or continued after their coronary episode) had similar sudden death rates, though mortality from non-sudden causes was considerably higher in those continuing to smoke. In this period non-smokers had the lowest sudden death rate (table 5).

Discussion

The World Health Organisation expert committee on sudden death concluded that "there is an urgent need to identify the various predisposing and precipitating factors that in the presence or absence of coronary heart disease and ischaemia may lead to fatal arrhythmias".[10] The purpose of the present study was to identify factors related to sudden death in survivors of an acute coronary episode followed for up to 18 years. Sudden death in the post-infarct patient over short follow up periods of a year or less[1] seems mainly related to ventricular arrhythmias and impaired left ventricular function. A recent editorial

Table 2 *Life table mortalities and percentages of sudden deaths (study group 551)*

		Cumulative mortality			
Time from initial episode (yr)	*No at risk (at end of period)*	*Total (%)*	*Sudden death (%)*	*Other vascular (%)*	*Non-vascular (%)*
0–2	500	9·3	5·5	3·6	0·2
2–5	430	21·3	11·6	7·5	2·2
5–10	270	39·4	18·9	15·5	5·0
10–15	63	63·2	28·2	26·0	9·0
15–18*	18	72·4	33·2	27·7	11·5

*There were six further deaths beyond this point

Table 3 *Average annual mortality and percentage of sudden deaths (95% confidence intervals are given in parentheses)*

	Average annual mortality		
Period after initial episode (yr)	*Total*	*Sudden death*	*Percentage of sudden deaths*
0–2	4·7 (3·5–6·0)	2·8 (1·8–3·7)	58·3 (44·8–71·9)
2–18	7·2 (6·3–8·0)	3·2 (2·6–3·8)	44·4 (38·2–50·5)

Table 4 *Age related to average annual mortality (95% confidence intervals are given in parentheses)*

Period after initial attack (yr)	*Age (yr)*	*Average annual mortality* *Total (%)*	*Other causes (%)*	*Sudden death (%)*	*Percentage of sudden deaths*
0–2	<45	4 8	1 0	3·8 (2·6–4·9)	79 (68–90)
	45–49	3·0	1 6	1 4 (0·7–2 1)	47 (34–61)
	50–54	4 0	2 4	1 6 (0 9–2 4)	41 (28–55)
	≥55	4 8	2 0	2 8 (1 9–3·8)	60 (46–73)
2–18	<45	3 8	1 4	2·4 (1 9–2·8)	63 (57–69)
	45–49	6 9	3 5	3 4 (2·8–4·0)	48 (42–55)
	50–54	7·6	4 5	3 1 (2 5–3 7)	41 (35–47)
	≥55	10 6	6 6	4 0 (3·3–4·7)	38 (32–44)

suggests, however, that ventricular tachycardia may be the initiating event.[11] Though many studies have reported on long term total mortality after infarction,[12] none seems to have studied the end point of sudden death in detail. In men free of overt coronary heart disease it has been shown that the risk factors for sudden death cannot be distinguished from the classic risk factors for the other manifestations of coronary heart disease.[13–15]

The identification of factors related to sudden death has important implications. Those with a high absolute risk should be advised to avoid situations, such as public service vehicle driving, where such an event could have serious consequences to themselves or others.[16] Patients at high risk of sudden death, especially in the early post-event period, may show greater benefit from prophylactic β blockade or other antiarrhythmic treatment,[17] although secondary prevention trials of such drugs still leave many unanswered questions about the use and efficacy of these agents. It is also not clear whether the reported mortality reductions in recent secondary prevention trials[18 19] are the result of the anti-ischaemic or antiarrhythmic effect of β blockers.[15]

In this study we have shown that sudden death in survivors of a coronary event becomes relatively less frequent as follow up increases. Aging seems to affect sudden death less than other modes of death, perhaps because the influence of the initial coronary event wanes with time. In fact over time the proportion of non-vascular and non-coronary deaths increased sharply. It should be emphasised that non-fatal reinfarction was not included as an end point in this analysis.

During the first two years after a coronary episode the younger patient is at particularly high risk of sudden death but not from other modes of death. The decreasing proportion of sudden deaths with age at initial attack, which was noted here only in those who survived the initial two years, has also been reported in those without coronary heart disease.[13] Hypertension, angina preceding the episode, and the severity of the initial attack were associated to the same degree with increased risks of sudden death and other modes and causes of death. The high sudden death rate and high proportion of sudden deaths in the non-smoker in the first two years are particularly surprising since among those without coronary heart disease non-smokers have a low risk of sudden death.[13] After two years, however, the sudden death rate in the initial non-smokers dropped significantly and it was also lower in this period than the rate in those who had ever smoked cigarettes. This might be attributable to the fact that those susceptible to sudden death in this group may have already died. The low sudden death rate in the current smokers in the first two years is difficult to explain.

In the later period of follow up the sudden death rate is similar in initial ex-smokers and current

Table 5 *Initial and follow up smoking habit related to average annual mortality (95% confidence intervals are given in parentheses)*

Period after initial attack (yr)	*Smoking habit*	*Average annual mortality* *Total (%)*	*Other causes (%)*	*Sudden death (%)*	*Percentage of sudden deaths*
0–2	Non	4 3	0 9	3·4 (2 3–4 5)	80 (69–91)
	Ex*	5 1	2 0	3 2 (2 2–4 3)	63 (49–76)
	Current	3·8	1·9	1 9 (1 1–2 7)	50 (36–63)
2–18	Non	4 8	3 2	1 6 (1·2–2 0)	33 (27–39)
	Ex*	5 7	2 2	3 5 (2 9–4 1)	61 (55–67)
	Stopped	6 7	3 4	3 3 (2 7–3·9)	49 (43–55)
	Continued	10 9	7 0	3 8 (3 1–4 6)	35 (29–41)

*Before initial attack.

smokers, irrespective of whether the latter continued or stopped smoking afterwards. The beneficial effect of stopping smoking on total mortality is not reflected in sudden death. This present analysis, corrected for the presence of other factors, did not include interaction terms in the regression model; thus the results cannot be compared directly with our previous report on the same patients.[20] We then showed that those who ceased smoking had a lower total mortality than the non-smokers and ex-smokers combined, and that stopping smoking reduced the rate of sudden death only in those with less severe coronary attacks.

In this study we have shown that in patients surviving a first episode of documented unstable angina or myocardial infarction the factors that relate to overall mortality also tend to influence sudden deaths. The proportion of sudden deaths decreases with age, however, and, unlike its effect on total mortality, stopping smoking does not reduce the absolute sudden death rate. The young patient and non-smoker are at particularly high risk of sudden death, especially in the first two years after an initial attack. Special attention with a view to prevention should be given to these groups.

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References

1 Schulze RA, Strauss HW, Pitt B. Sudden death in the year following myocardial infarction. *Am J Med* 1977;**62**:192–9.

2 Roelandt J, Hugenholtz PG. Sudden death: prediction and prevention. *Eur Heart J* 1986;7 (suppl A):169–80.

3 Rosenthal ME, Oseran DS, Gang E, Peter T. Sudden cardiac death following acute myocardial infarction. *Am Heart J* 1985;**109**:865–76.

4 Mulcahy R, Hickey N, Graham I, McKenzie G. Factors influencing long-term prognosis in male patients surviving a first coronary attack. *Br Heart J* 1975;**37**:158–65.

5 Ronan G, Ruane P, Graham I, Hickey N, Mulcahy R. The reliability of smoking history amongst survivors of myocardial infarction. *Br J Addict* 1981;**76**:425–8.

6 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association* 1958;**53**:457–81.

7 Cox DR. Regression models and life tables. *Journal of the Royal Statistical Association* 1972;**B34**:187–220.

8 *SUGI Supplemental Library Users' Guide* Version 5 edition. Cary, NC: SAS Institute, 1986:437–66.

9 Chiang CL. On the probability of death from specific causes in the presence of competing risks. *Proceedings of the Fourth Berkeley Symposium* 1961;**4**:169–80.

10 WHO Scientific Group. Sudden cardiac death. *WHO Tech Rep Ser* No 726. 1985.

11 Buxton AE. Sudden cardiac death—1986. *Ann Intern Med* 1986;**104**:716–8.

12 Graham I, Mulcahy R, Hickey N, O'Neill W, Daly L. Natural history of coronary heart disease: a study of 586 men surviving an initial acute attack. *Am Heart J* 1983;**105**:249–57.

13 Kannel WB, Doyle JT, McNamara PM, Quickenton P, Gordon T. Precursors of sudden death: factors related to the incidence of sudden death. *Circulation* 1975;**51**:606–13.

14 Schatzkin A, Cupples A, Heeren T, Morelock S, Mucatel M, Kannel WB. The epidemiology of sudden unexpected death. risk factors for men and women in the Framingham Heart Study. *Am Heart J* 1984;**107**:1300–6.

15 Cobbe SM. Sudden cardiac death and acute coronary thrombosis. *Br Med J* 1985;**290**:93–4.

16 Robinson K, Mulcahy R. Return to employment of professional drivers following myocardial infarction. *Ir Med J* 1986;**79**:31–4.

17 May GS, Eberlein KA, Furberg CD, Passamani ER, DeMets DL. Secondary prevention after myocardial infarction: a review of longterm trials. *Prog Cardiovasc Dis* 1982;**24**:331–52.

18 The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;**304**:801–7.

19 β-Blocker heart attack trial research group: a randomised trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;**247**:1707–14

20 Daly LE, Mulcahy R, Graham IM, Hickey N. Long-term effect on mortality of stopping smoking after unstable angina and myocardial infarction. *Br Med J* 1983;**287**:324–6.

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Mortality in heart failure: clinical variables of prognostic value

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SUMMARY One hundred and fifty two patients with chronic heart failure caused primarily by left ventricular dysfunction were followed prospectively in an open study for a mean period of 21 months. The effects of several clinical variables on subsequent outcome were examined, including the effects of treatment, which was determined by the clinician caring for the patient and was *not* randomly allocated. In order of importance, frequent ventricular extrasystoles, non-treatment with amiodarone, low mean arterial pressure, and a diagnosis of coronary artery disease were associated with a poor prognosis, with each of these variables providing extra predictive information independently of the others. Initial serum potassium concentration and treadmill exercise time also carried further weak but independent prognostic information. Neither treatment with angiotensin converting enzyme inhibitors nor digoxin appeared to affect outcome. Left ventricular function (as reflected by M mode echocardiography) and the dose of diuretic also failed to predict outcome. There did, however, appear to be a reduction in the frequency of sudden death when angiotension converting enzyme inhibitors were given.

Further studies are required to confirm the adverse prognostic significance of ventricular arrhythmias in patients with heart failure and the possible benefit associated with amiodarone treatment.

Chronic heart failure is a condition of varied aetiology that imposes a heavy burden of symptoms, confers a very poor prognosis,[1-3] and affects 4% of the population under the age of 75 years.[4] Once an in-hospital diagnosis of heart failure has been made, the annual mortality is likely to be 40% or more,[1-3] though the prognosis seems to be slightly better in those patients not referred to hospital and who, presumably, have milder disease.

The most frequently reported mode of death in patients with heart failure seems to be sudden,[2 3 5] presumably caused by ventricular arrhythmias,[6] which are common.[1 7 8] Many[1 9 10] but not all[11-13] workers suggest that these arrhythmias are powerful independent prognostic indicators for mortality. Whether they are of primary importance or merely reflect the extent of left ventricular dysfunction is unclear at present.[1 10 13] One retrospective case-control study suggested no reduction in mortality with procainamide,[14] though anecdotal comment has suggested a possible benefit with amiodarone.[15] Another prospective study suggested that arrhythmias in patients with heart failure are resistant to treatment.[16] "Vasodilator" treatment on the other hand has been shown to improve outcome.[17 18]

We investigated the importance of arrhythmias, left ventricular function, treatment, functional capacity, and biochemical indices in predicting outcome in a large series of patients with heart failure followed prospectively in an open study.

Patients and methods

PATIENTS

One hundred and fifty two patients in whom a diagnosis of heart failure was established on clinical, radiological, and echocardiographic grounds were recruited. All were symptomatically stable but in New York Heart Association classes II–IV (mean (1 SD) 2·8 (0·8)). The mean (1 SD) age was 59 (9)

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years, 84% were male, and the mean (SD) duration of heart failure was 18 (19) months (all > 3 months).

One hundred and four had received digoxin for more than one month before entry to the study and all were receiving frusemide in a mean (1 SD) daily dose of 127 (85) mg/day. No patients were on potassium-sparing diuretics but 47 were on potassium chloride supplements (median dose 1800 mg/day).

The diagnosis was ischaemic heart disease in 93, idiopathic congestive (dilated) cardiomyopathy in 28, residual left ventricular dysfunction after successful valve replacement in 16, secondary to hypertension in nine, and alcohol related cardiomyopathy in six. Patients in whom angina was an appreciable complaint at rest or during exercise were excluded. The absence of coronary artery disease was always confirmed by coronary angiography; coronary artery disease was diagnosed either at coronary angiography or after myocardial infarction with typical history and electrocardiographic and enzyme changes.

Patients were allocated to angiotensin converting enzyme inhibitors or amiodarone on an open basis, either in the context of a clinical trial[19] or for clinical reasons on the order of the attending physician. Selection of patients was not systematic and criteria varied over the period of observation. Patients were therefore not necessarily selected for angiotensin converting enzyme inhibitors or treatment with amiodarone on the basis of severity of heart failure or the presence of arrhythmias. This reflects the uncertainty of the clinical value of these drugs during much of the observation period. Amiodarone was started at 200 mg three times a day in most cases, with a mean (1 SD) daily maintenance dose of 183 (54) mg/day (range 100–400 mg/day).

METHODS

New York Heart Association scores were determined in the light of the exercise performance. Heart rate was measured from the apex beat and blood pressure was recorded with a Hawkesley random zero sphygmomanometer.

A 12 lead electrocardiogram was recorded before a graded treadmill test by a modified Bruce protocol. Forty eight hour ambulatory monitoring was also performed with a Medilog I system and the results were analysed with a Pathfinder Analyser under constant visual monitoring. Ventricular tachycardia was defined as $\geqslant 3$ consecutive ventricular extrasystoles at > 120 beats/minute.

M mode echocardiography was performed with the patients in the left lateral position.

Blood was taken for measurement of serum sodium, potassium, and creatinine concentrations on at least two and up to five occasions at different times of day and an average value was taken. The median number of samples taken was three. Blood was taken for measurement of serum digoxin concentration at least six hours after the last dose.

DEFINITION OF MODES OF DEATH

The mode of death was ascertained either from the deceased's relatives, from the family practitioner, or from the observations of the hospital staff. Where death was believed to be from cardiac causes, it was classified as death from pulmonary oedema, cardiogenic shock, or sudden (defined as death without reporting a change in symptoms in the 24 hours before death to lay or medical persons). Sudden death was also divided into cases that had or had not indicated some gradual chronic deterioration of symptoms of heart failure in the months before death.

STATISTICAL ANALYSIS

Means (1 SD) are given for the study group and treatment subgroups. Means of subgroups were compared by two-sample t tests. The log-rank test[20] was used to compare survival rates in the treatment subgroups. Cox's proportional hazards model[21] was used to correct for and identify important covariates. A stepwise routine[22] was used to identify the best subset of predictors. Both forward and backward stepping was used to protect against the omission of important predictors. Pearson's product moment correlation coefficients were calculated to investigate interrelations between the prognostic indicators and the other variables. Estimated survival curves were subsequently constructed for each treatment and for each of the variables independently related to outcome. This was done by fixing at median values all variables that carried independent predictive information other than the one tested.

Results

CLINICAL OUTCOME

The mean follow up time was 21 (12) months, during which 63 patients (41%) died. Forty seven (75%) of the deaths were sudden, though in 12 (26%) patients clinical deterioration was noted at the follow up clinic in the months before death. Five patients died in cardiogenic shock after recurrent myocardial infarction and two died after cerebrovascular accidents. One patient died after mesenteric artery occlusion, one soon after peripheral vascular surgery, one from chronic lymphatic leukaemia and associated respiratory infection, and one from rectal carcinoma. Only five (8%) deaths were considered to be caused by intractable left ventricular failure. Four patients presented with sustained ventricular tachycardia during follow up. None was on antiarrhythmic treatment at the time. Although treatment with procainamide in two cases, tocainide in one case, and amiodarone in one case was started, all four subsequently died.

PREVALENCE OF ARRHYTHMIAS

The mean frequency of ventricular extrasystoles over 24 hours was 4321 (median value 1375, range 0–24299). Seventy nine per cent of patients had couplets or salvoes of ventricular extrasystoles on ambulatory monitoring (mean 15, median 5, range 0–768 per 24 hours). Sixty one per cent of patients had one or more episodes of ventricular tachycardia with a mean overall frequency of seven (median value 2, range 0–201) in 24 hours.

BASELINE CHARACTERISTICS

The mean initial heart rate was 88 (14) beats/min and mean arterial pressure was 91 (14) mm Hg. Forty five patients (30%) had left bundle branch block. The mean concentration of serum sodium was 136 + 10 mmol/l, of serum potassium 3·8 (0·4) mmol/l, and of serum creatinine 117 (27) μmol/l. The mean end diastolic left ventricular dimension was 6·7 (0·8) cm and end systolic dimension was 5·7 (0·9) cm. The resulting fractional shortening was 15·3 (6·5)%.

CHANGES IN TREATMENT

During follow up 11 patients were started on nitrate treatment, one on prazosin, and three on hydralazine. In 18 patients an increase in diuretic treatment was required, and in six patients who were taking angiotensin converting enzyme inhibitors the dose of diuretic was reduced because of postural hypotension. As mentioned above four patients were treated with antiarrhythmic agents for sustained ventricular tachycardia at a time other than entry to the study. Nineteen patients were taking potassium-sparing diuretics: amiloride in 14 (10–20 mg/day) and spironolactone in five (25–50 mg/day). Only three of these were in the group treated with angiotensin converting enzyme inhibitors.

COMPARISON OF TREATMENT SUBGROUPS

Those treated with amiodarone were well matched in all respects with those who did not receive this treatment (table 1). Those subjects treated with angiotensin converting enzyme inhibitors (table 2) had significantly worse New York Heart Association scores, tended to have shorter exercise times, more episodes of ventricular tachycardia, and required significantly more frusemide and digoxin.

Patients taking digoxin (table 3) had worse New York Heart Association scores than those not on digoxin.

Table 1 *Comparison between patients taking amiodarone and those not taking amiodarone*

Data	*No amiodarone*	*Amiodarone*
No	111	41
Age (yr)	60 (10)	58 (8)
Sex (% males)	82	88
NYHA	2·8 (0·8)	2·9 (0·9)
CAD (%)	60	66
Exercise time (min)	7·5 (4·8)	7·4 (4·6)
MAP (mm Hg)	91 (14)	92 (14)
FS (%)	15·6 (6·8)	14·6 (5·7)
Left BBB (%)	32	24
Serum sodium (mmol/l)	137 (5)	137 (4)
Serum potassium (mmol/l)	3·8 (0·4)	3·9 (0·4)
Ventricular extrasystoles	4261	4462
(24 hr)	range 6–24299	range 7–17345
Ventricular tachycardia	4·8	11·4
(24 hr)	range 0–67	range 0–201
ACE inhibitor (No)	43	18
Digoxin (No)	74	30
Frusemide (mg/day)	128 (93)	122 (61)

Values are mean (1 SD), or range. ACE, angiotensin converting enzyme, NYHA, New York Heart Association functional class; CAD, coronary artery disease; MAP, mean arterial pressure; FS, echocardiographic left ventricular fractional shortening; BBB, bundle branch block.

PREDICTORS OF PROGNOSIS

Several variables were found to be of prognostic value by Cox's proportional hazards model (table 4). Stepwise regression with Cox's proportional hazards model showed that in order of importance ventricular extrasystoles ($p < 0\cdot0001$), amiodarone treatment ($p < 0\cdot001$), mean blood pressure (p <

Table 2 *Comparison between patients taking an ACE inhibitor and those not taking an ACE inhibitor*

Data	*No ACE inhibitor*	*ACE inhibitor*
No	91	61
Age (yr)	59 (10)	59 (8)
Sex (% males)	89	75
NYHA†	2·6 (0·7)	3·1 (0·8)
CAD (%)	65	56
Exercise time (min)	8·0 (4·5)	6·6 (5·0)
MAP (mm Hg)	93 (15)	88 (13)
FS (%)	16·1 (6·3)	14·3 (6·7)
Left BBB (%)	32	27
Serum sodium (mmol/l)	137 (8)	136 (6)
Serum potassium (mmol/l)	3·9 (0·4)	3·7 (0·4)
Ventricular extrasystoles	4121	4592
(24 hr)	range 0–21804	range 0–24299
Ventricular tachycardia	4·4	10
(24 hr)	range 0–38	range 0–201
Amiodarone (No)	23	18
Digoxin (No)*	49	55
Frusemide (mg/day)‡	101 (54)	163 (106)

See footnote to table 1 for abbreviations.

*$p < 0\cdot05$. †$p < 0\cdot01$. ‡$p < 0\cdot001$.

Table 3 *Comparison between patients taking digoxin and those not taking digoxin*

Data	*No digoxin*	*Digoxin*
No	48	104
Age (yr)	59 (11)	60 (9)
Sex (% males)	89	80
NYHA*	2·5 (0·7)	3·0 (0·8)
CAD (%)	50	67
Exercise time (min)	8·0 (4·5)	7·0 (4·7)
MAP (mm Hg)	93 (13)	90 (15)
FS (%)	16·6 (6·3)	14·8 (6·5)
Left BBB (%)	37	29
Serum sodium (mmol/l)	138 (5)	136 (5)
Serum potassium (mmol/l)	4·0 (0·4)	3·8 (0·4)
Ventricular extrasystoles	3452	4692
(24 hr) range	6–21804	range 7–24299
Ventricular tachycardia	4·7	7·6
(24 hr) range	0–38	range 0–201
Amiodarone (No)	11	30
ACE inhibitor (No)†	6	55
Frusemide (mg/day)	93 (58)	143 (92)

See footnote to table 1 for abbreviations.
*p < 0·03. †p < 0·01.

0·001), and a diagnosis of coronary artery disease ($p < 0{\cdot}001$) were of important independent prognostic value. Initial serum potassium concentration ($p < 0{\cdot}02$) and exercise time ($p < 0{\cdot}03$) were found to be of some additional independent predictive value.

EFFECTS OF TREATMENT

Amiodarone treatment seemed to improve the prognosis ($p < 0{\cdot}01$) (fig 1); this reduction in mortality was largely caused by a decline in the occurrence of sudden death, as 45% of those not treated with amiodarone died suddenly compared with 15% of those treated with amiodarone during the follow up period. While angiotensin converting enzyme inhibitors had no overall beneficial effect on mortality (fig 2), the frequency of sudden death was less (21% *vs* 37%; $p < 0{\cdot}05$). There were six (10%) deaths (see above) caused by vascular events in the group on angiotensin converting enzyme inhibitors but only three (3%) in the group not treated with angiotensin converting enzyme inhibitors (NS). Treatment with digoxin (fig 3) and diuretic dose did not alter the overall prognosis or the frequency of sudden death before or after adjustment for the covariates. Separate analysis of those patients undergoing a change in treatment showed no alteration in prognosis. Potassium supplements did not affect prognosis.

Table 4 *Prognostic value of variables analysed by Cox's proportional hazards model (univariate analysis)*

Variable	*Statistical significance*
Ventricular extrasystoles (24 h)	p < 0·0001
Mean arterial pressure (mm Hg)	p < 0·0001
Serum potassium (mmol/l)	p < 0·0001
Serum sodium (mmol/l)	p < 0·0001
Exercise time (min)	p < 0·0001
NYHA score	p < 0·0001
Amiodarone treatment	p < 0·01
Echocardiographic end systolic dimension (cm)	p < 0·01
Echocardiographic fractional shortening (%)	p < 0·01
Left bundle branch block	p < 0·01
Echocardiographic end diastolic dimension (cm)	p < 0·02
Diagnosis of coronary artery disease	p < 0·06
Ventricular tachycardia (/24 h)	p < 0·06
Age (years)	p < 0·07
Frusemide dose (mg/day)	p < 0·1
Duration of symptoms	p < 0·7
Heart rate (beats/min)	p < 0·8
Captopril treatment	p = 0·93
Digoxin treatment	p = 0·99

RELATION OF VENTRICULAR EXTRASYSTOLES TO OTHER MEASURED VARIABLES

Ventricular extrasystoles were correlated with the frequency of more complex ventricular extrasystoles ($r = 0{\cdot}66$; $p < 0{\cdot}0001$) and were also associated with a worse New York Heart Association score ($p < 0{\cdot}001$). However, no association was noted with the use of digoxin or with concentrations of serum digoxin (0·8–2·3 nmol/l) (all of which were in the therapeutic range < 2·6 nmol/l). Exercise time ($r = -0{\cdot}45$ $p < 0{\cdot}001$), serum potassium ($r = -0{\cdot}38$

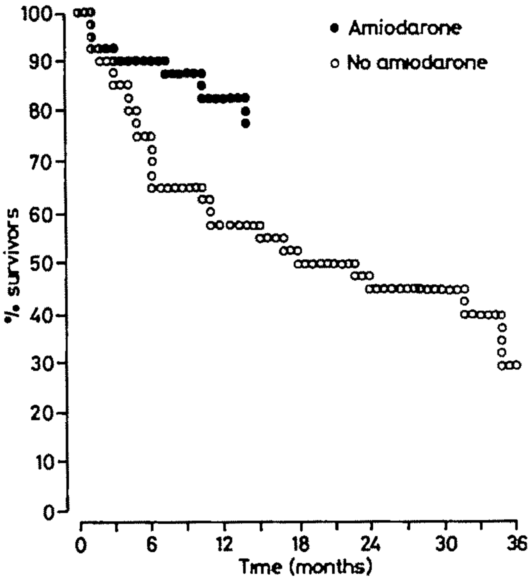

Fig 1 *Cumulative proportion surviving (log rank test). Patients on amiodarone faired better (p < 0·01). Note that no events occurred in the amiodarone treated patients after 15 months and no valid prediction of subsequent mortality can be made from this analysis.*

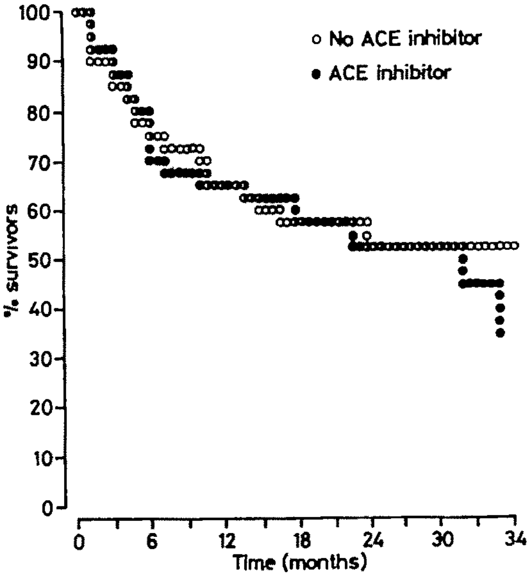

Fig 2 *Log rank survival curves comparing patients treated with or without angiotensin converting enzyme inhibitors. No difference was noted.*

p < 0·001), and left bundle branch block (r = 0·35 p < 0·001) were the best predictors of the frequency of ventricular arrhythmias.

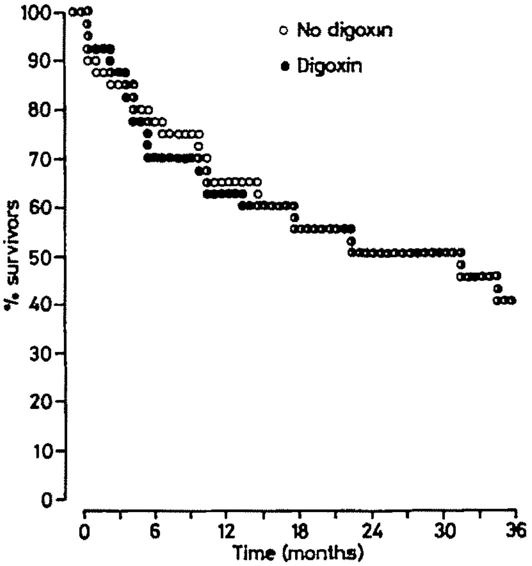

Fig 3 *Log rank survival curves comparing patients treated with or without digoxin. No difference was noted.*

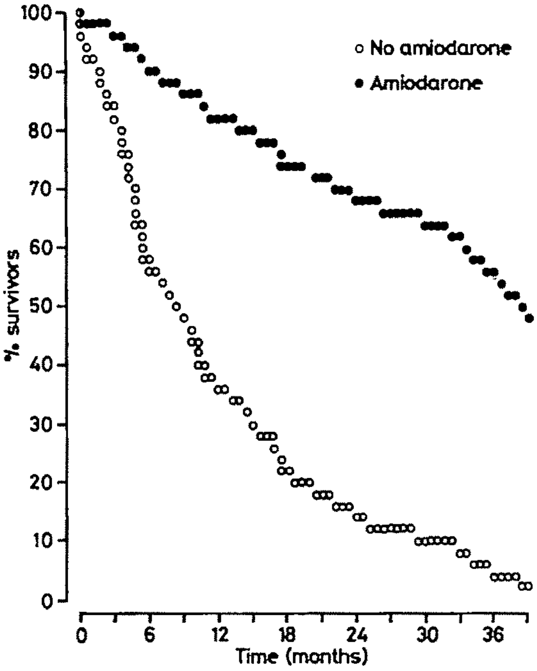

Fig 4 *Estimated survival function of patients with or without amiodarone treatment. The frequency of ventricular extrasystoles, the mean arterial pressure, serum potassium, and exercise time were all fixed at median values and all patients were designated as having coronary artery disease (the largest diagnostic subgroup).*

COMPARISON OF RISK FACTORS IN DIAGNOSTIC SUBGROUPS

Those subjects with heart failure caused by coronary artery disease had a significantly lower blood pressure than those without coronary artery disease (89 (12) *vs* 94 (16) mm Hg; p < 0·01) and a lower frequency of ventricular arrhythmias (3950 *vs* 4875/24 hours; p < 0·02). The duration of symptoms before entry was also shorter (12·9 (14·7) *vs* 25·7 (21·1) months; p < 0·01). In other respects, including ventricular function (fractional shortening 15·5 (6·3)% *vs* 15·0 (6·8)%), exercise time (7·5 (4·6) *vs* 7·4 (4·9) minutes), and serum potassium (3·9 (0·4) *vs* 3·8 (0·4) mmol/l) they were similar to patients in other diagnostic groups.

RELATION OF MEAN ARTERIAL PRESSURE TO OTHER MEASURED VARIABLES

The set of variables with the best independent relation to mean arterial pressure was serum sodium (r = 0·54 p < 0·001), New York Heart Association score (r = −0·41 p < 0·001), and end diastolic left ventricular dimension (r = −0·29 p < 0·01).

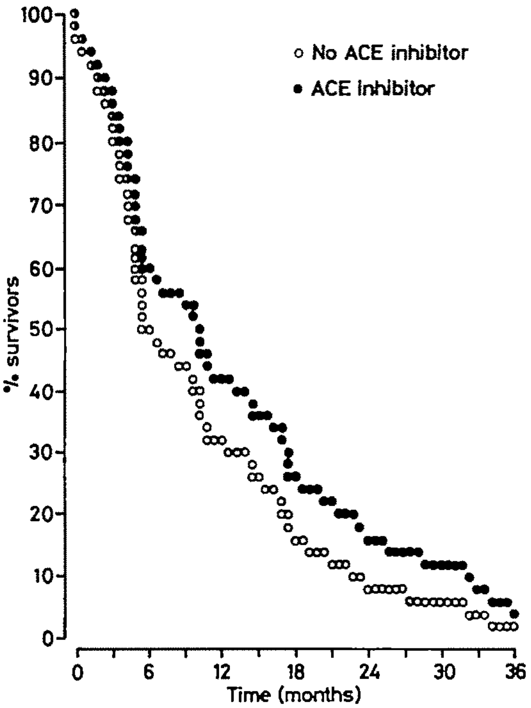

Fig 5 *Estimated survival curve for patients with or without angiotensin converting enzyme inhibitors. Again all important prognostic factors were fixed at median values; patients were designated as having coronary artery disease but not receiving amiodarone.*

RELATION OF SERUM POTASSIUM AND EXERCISE TIME TO OTHER MEASURED VARIABLES

Only serum sodium ($r = 0{\cdot}40$ $p < 0{\cdot}001$) was found to have a significant and independent relation to serum potassium. Exercise time was best related on stepwise regression to New York Heart Association score ($r = -0{\cdot}79$; $p < 0{\cdot}0001$) and fractional shortening ($r = 0{\cdot}31$; $p < 0{\cdot}001$).

ESTIMATED SURVIVAL CURVES

The estimated survival curves for amiodarone versus no amiodarone treatment again suggested significant improvement in survival with amiodarone (fig 4). The estimated survival curves still suggested no pronounced beneficial effect with angiotensin converting enzyme inhibitors (fig 5), but also suggested no deleterious effect with digoxin use.

The estimated survival curves for prognostic indicators suggested that clinically meaningful separation could be made on the basis of the frequency of ventricular extrasystoles (fig 6), a diagnosis of coronary artery disease (fig 7), mean arterial pressure (fig 8), exercise time (fig 9), and serum potassium (fig 10).

Discussion

Several recent studies in populations of patients with heart failure with varying diagnoses have reported conflicting results for the most reliable independent indicators of prognosis.[1 3 13] Some suggest that ventricular arrhythmias are the most powerful independent indicators[1 5 7] but others have not confirmed this.[11–13] It may be that ventricular arrhythmias merely reflect the extent of left ventricular dysfunction.[5 10 13 23] These different views may be a reflection of different study populations, with arrhythmias in heart failure caused by idiopathic dilated cardiomyopathy showing a good relation with the extent of left ventricular dysfunction in some studies[24] but not in others.[13] In patients with ischaemic heart disease and left ventricular dysfunction, arrhythmias seem to be poorly related to the extent of dysfunction.[7 10] Some studies suggest that indices of cardiac function and the severity of symptoms are helpful in predicting the prognosis of

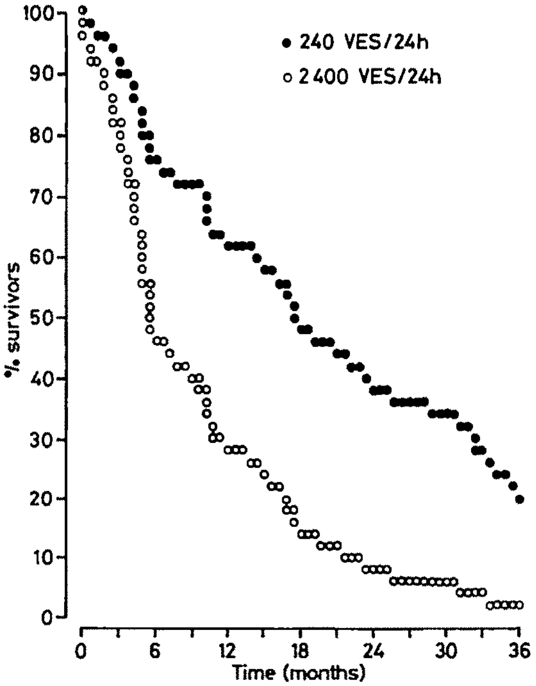

Fig 6 *Estimated survival curve for patients with a high and a low frequency of ventricular extrasystoles (VES). Values were chosen arbitrarily. Patients had other important prognostic factors fixed at median values and were assumed to have coronary artery disease but not to be taking amiodarone.*

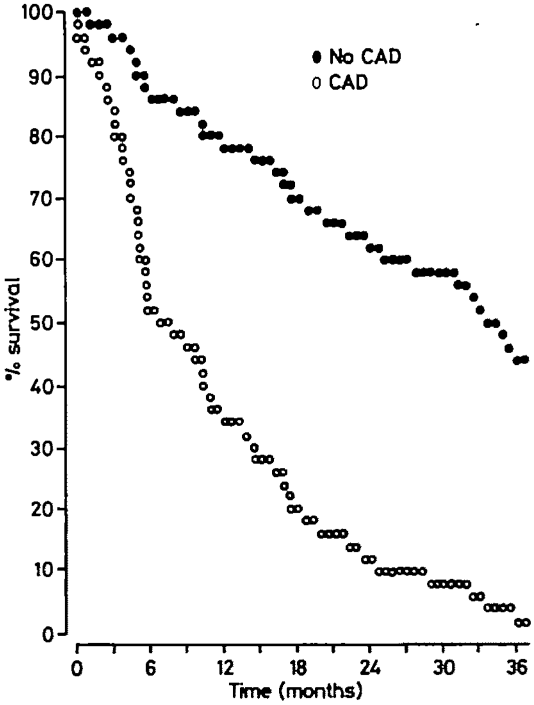

Fig 7 *Estimated survival curve for patients with or without coronary artery disease. Patients had other important prognostic factors fixed at median values and were assumed not to be taking amiodarone.*

patients with heart failure.[2 12 25] Left bundle branch block[5 26] serum sodium concentration,[3 27] mean arterial pressure,[2] exercise performance,[28] and central venous plasma noradrenaline concentration[3] have also been found to be useful in some studies. But for each of these indices there are conflicting studies.[29–31]

This study clearly demonstrates that the frequency of ventricular extrasystoles is strongly associated with a poor prognosis in patients with chronic heart failure caused by left ventricular dysfunction. That death is due to ventricular arrhythmias cannot be proved in a study like this one, but the high frequency of sudden death and low frequency of death caused by intractable heart failure suggest that the great majority of deaths in such patients are the result of arrhythmias. The lack of a significant relation between more complex ventricular arrhythmias and mortality may reflect the relatively short period over which we recorded the electrocardiogram. We have confirmed that complex ventricular arrhythmias relate closely to the frequency of simple extrasystoles, as has been previously noted.[1]

The frequency of sudden death in this study is higher than the figure of around 50% reported in some studies. This may reflect differences in both the chosen patient population and differences in reporting. Other investigators have tended to exclude from the sudden death group patients with some deterioration in their condition before death, though the terminal event may none the less have been sudden, unexpected, and potentially arrhythmic. On the other hand we have adopted a very rigid definition of death caused by heart failure.

Our study suggests that arrhythmias are more closely related to functional class and exercise performance than to indices of resting left ventricular performance. The lack of a relation between prognosis and M mode echocardiographic measurements of left ventricular function should be interpreted with caution especially when comparing different subjects with ventricles that have been damaged by ischaemia. However, several studies with invasive haemodynamics have also suggested a poor relation with prognosis.[2 5] The relatively poor relation of exercise performance to left but not to right ventric-

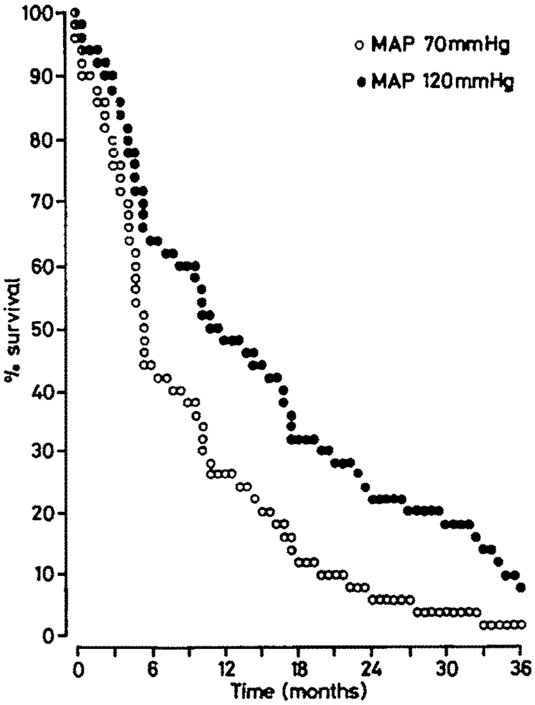

Fig 8 *Estimated survival curve for patients with a high or a low mean arterial pressure (MAP). Values were chosen arbitrarily. Patients had other important prognostic factors fixed at median values and were assumed to have coronary artery disease but not to be taking amiodarone.*

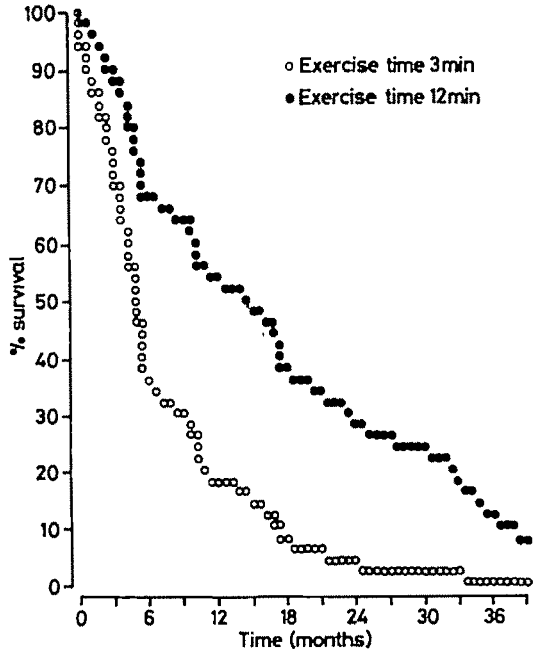

Fig 9 *Estimated survival curve for patients with a short or a long exercise time in the modified Bruce protocol. Values were chosen arbitrarily. Patients had other important prognostic factors fixed at median values and were assumed to have coronary artery disease but not to be taking amiodarone.*

ular haemodynamic function has been well documented.[32 33] The relation between exercise performance and prognosis may suggest this is a better index of cardiac performance.[28]

Hypokalaemia was more closely associated with ventricular arrhythmias than has been suggested previously,[34] though a direct causal relation cannot be confirmed. The association may have been increased by use of digoxin,[35–37] since hypokalaemia may enhance myocardial digoxin binding.[36] Hypokalaemia may also be an index of depletion of total body reserves of potassium.[38 39]

We were unable to demonstrate any direct effect of therapeutic concentrations of digoxin on arrhythmias in heart failure, perhaps because of the wide interindividual susceptibility to arrhythmias or to the counterbalancing effect of an improvement in left ventricular function.[40]

It is likely that local myocardial ultrastructural and metabolic factors together with focal ischaemia caused by coronary vascular disease or excessive myocardial wall tension also lead to arrhythmias; these would not have been detected by our screening methods. Increased sympathetic activity might also give rise to arrhythmias[41] and because sympathetic activity appears greatest in subjects with the lowest mean arterial pressure[42] this is one mechanism by which low blood pressure may be related to arrhythmias.

A low mean blood pressure was also found to be of prognostic significance, as has been noted by others.[2] Plasma renin and catecholamines are known to be inversely related to blood pressure in heart failure[42] and a recent study has suggested that concentrations of plasma noradrenaline and to a lesser extent plasma renin are of prognostic significance in heart failure,[3] though this has been disputed.[7] Our study also demonstrates the inverse relation between blood pressure and serum sodium. Low blood pressure appears also to be a marker of clinically more severe heart failure because it is associated with worse New York Heart Association scores and poorer exercise performance.

The poorer prognosis in patients with coronary artery disease noted in this and other studies[2] appears related to sudden death rather than reinfarction. Transient focal ischaemia may have caused arrhythmias even though angina was not a feature of this study group. The shorter duration of symp-

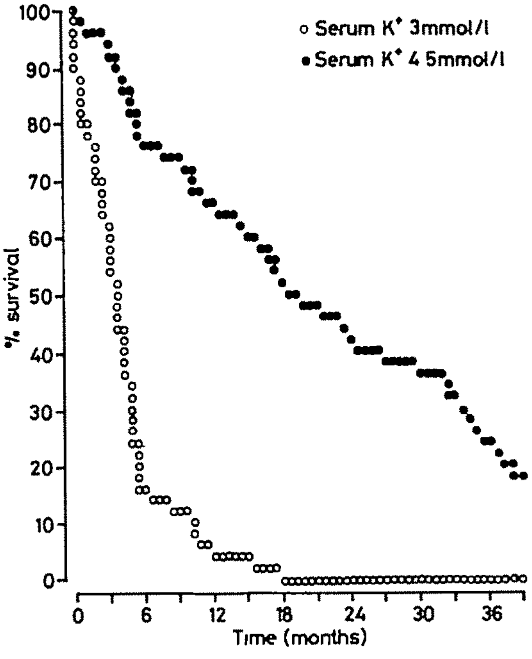

Fig 10 *Estimated survival curve for patients with a high or a low initial mean serum concentration of potassium. Values were chosen arbitrarily. Patients had other important prognostic factors fixed at median values and were assumed to have coronary artery disease but not to be taking amiodarone.*

toms, lower mean blood pressure, and lower incidence of arrhythmias in those with coronary artery disease should also be noted.

The widely divergent estimated survival curves that we found not only for amiodarone treatment, but also for the frequency of ventricular arrhythmias, the diagnosis of coronary artery disease, arterial pressure, exercise time, and serum potassium suggest that the factors we have described are of clinical relevance. These clinical variables could be used to define an individual patient's likely prognosis.

The effect of vasodilators on prognosis remains controversial,[17 43 44] while angiotension converting enzyme inhibitors appear to have beneficial effects on prognosis.[18 43 45] Attempts have been made with antiarrhythmic drugs to improve the prognosis in heart failure. Some drugs such as disopyramide[46] and flecainide[47] seem to be unsuitable because of their negative inotropic action, while experience with other class I agents such as procainamide[14] has not been fruitful. Agents such as β blockers and verapamil[48 49] are also negative inotropes; these also seem unsuitable for use in this area, though there is conflicting evidence of a beneficial effect of β blockers in heart failure.[50 51]

Depression of ventricular function by amiodarone at rest or during exercise is rare when modest doses are used.[52 53] Amiodarone also effectively suppresses ventricular arrhythmias in patients with heart failure,[17] presumably accounting for the pronounced reduction in sudden death. The improvement in prognosis noted in the present study may not be entirely the result of its antiarrhythmic actions. Amiodarone also has antiischaemic effects which may be beneficial in idiopathic dilated cardiomyopathies as well as in heart failure related to coronary artery disease.

The relatively low maintenance dose of amiodarone used in this study limited the frequency of side effects. We have also noted worsening of arrhythmias in patients with heart failure when a loading dose of amiodarone of 200 mg three times a day was given. Such patients have responded to a more gradual introduction of amiodarone 100–200 mg once daily. Though the PR interval was prolonged in several patients on amiodarone we found only one case of higher grade block (2:1 block).

We were unable to demonstrate any effect on overall prognosis associated with the use of either digoxin or angiotensin converting enzyme inhibitors, nor did the dose of diuretic exert any powerful effect. The group treated with angiotensin converting enzyme inhibitors had worse heart failure, however, and the statistical analysis may not have compensated for this difference. A large controlled study has demonstrated a pronounced reduction in mortality rates in patients with very severe heart failure treated with enalapril.[18] Interestingly, in patients with severe heart failure deaths from progressive heart failure were reduced but not sudden deaths. This contrasts with the rise in mortality associated with the use of some inotropic agents in heart failure.[54] In our study, the incidence of sudden death was significantly reduced in those on angiotensin converting enzyme inhibitors; this may have been attributable to correction of hypokalaemia and hypomagnesaemia and intracellular potassium depletion, beneficial haemodynamic effects, and a reduction in sympathetic activity.[55 56] The statistically insignificant increase in the frequency of vascular events suggests that angiotensin converting enzyme inhibitors should be used with caution in patients with known critical arterial stenoses. Potential deleterious effects of digoxin and higher doses of diuretics may have been masked by the use of amiodarone and captopril, but they did not seem to exert any powerful influence on prognosis.

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References

1 Meinertz T, Hofmann T, Kasper W, *et al.* Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1984;53:902–7.

2 Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary artery disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983;51:831–6.

3 Cohn JN, Levine TB, Olivari MT, *et al.* Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819–23.

4 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;285:1441–6.

5 Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy. *Am J Cardiol* 1984;54:147–52.

6 Milner PG, Platia EV, Reid PR, Griffith LSC. Ambulatory electrocardiographic recordings at the time of fatal cardiac arrest. *Am J Cardiol* 1985;56:588–92.

7 Holmes J, Kubo SH, Cody RJ, Kligfield P. Arrhythmias in ischaemic and nonischaemic dilated cardiomyopathy; prediction of mortality by ambulatory electrocardiography. *Am J Cardiol* 1985;55:146–51.

8 McKenna WJ, Krikler DM, Goodwin JF. Arrhythmias in dilated and hypertrophic cardiomyopathy. *Med Clin North Am* 1984;**68**:983–1000.

9 Shugoll GI, Bowen PJ, Moore JP, Lenkin ML. Follow up observations and prognosis in primary myocardial disease. *Arch Intern Med* 1972;**129**:67–72.

10 Bigger JT, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationship among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;**68**:250–8.

11 Shirey EK, Proudfit WL, Hawk WA. Primary myocardial disease. Correlation with clinical findings, angiographic and biopsy diagnosis. Follow up of 139 patients. *Am Heart J* 1980;**99**:198–207.

12 Wilson JR, Schwartz JS, Sutton MSJ, *et al.* Prognosis in severe heart failure: relation to haemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;**2**:403–10.

13 Von Olshausen K, Schafer A, Mehmel HC, Schwarz F, Senges J, Kübler W. Ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Br Heart J* 1984; **51**:195–201.

14 Chakko CS, Gheorghiade M. Ventricular arrhythmias in severe heart failure: incidence, significance, and effectiveness of antiarrhythmic therapy. *Am Heart J* 1985;**109**:497–504.

15 Mestroni L, Fonda F, Camerini F. Ventricular arrhythmias in congestive cardiomyopathy. *N Engl J Med* 1983;**309**:377–8.

16 Poll DS, Marchlinski FE, Buxton AE, Doherty JU, Waxman HL, Josephson ME. Sustained ventricular tachycardia in patients with idiopathic dilated cardiomyopathy: electrophysiologic testing and lack of response to antiarrhythmic drug therapy. *Circulation* 1984;**70**:451–6.

17 Cohn JN, Archibald DGA, Ziesche S, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med* 1986;**314**: 1547–52.

18 The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;**316**:1429–35.

19 Cleland JGF, Dargie HJ, Findlay IN, Wilson JT. Clinical, haemodynamic, and antiarrhythmic effects of long term treatment with amiodarone of patients in heart failure. *Br Heart J* 1987;**57**:436–45.

20 Peto R, Peto J. Asymptotically efficient rank invariant procedures. *J Roy Statist Soc* 1972;**135**(series A). 185–207.

21 Cox DR. Regression models and life tables. *J Roy Statist Soc* 1972;**136**(series B):187–220.

22 BMDP. *BMDP statistical software*. Los Angeles: University of California Press, 1983.

23 Glover DR, Littler WA. Factors influencing survival and mode of death in severe chronic ischaemic heart disease. *Br Heart J* 1987;**57**:125–32.

24 Diaz R, Obasohan A, Newman H, Goodwin JF, Oakley C. Prognostic indicators in dilated cardiomyopathy [Abstract]. *Br Heart J* 1985;**53**:114.

25 Fuster V, Gersh B, Giuliani G, Tajik A, Brandenburg R, Frye R. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981;**47**:525–31.

26 Convert G, Delaye J, Beaune J, Biron A, Gonin A. Prognosis of primary non-obstructive cardiomyopathies. *Arch Mal Coeur* 1980;**73**:227–37.

27 Lee WH, Packer M. Prognostic value of serum sodium concentration in severe heart failure and its modification by converting enzyme inhibition [Abstract]. *Circulation* 1984;**70**(suppl II):II–113.

28 Szlachic J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. *Am J Cardiol* 1985;**55**:1037–42.

29 Graboys TB, Lown B, Podrid PJ, DeSilva R. Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. *Am J Cardiol* 1982;**50**:437–43.

30 Follansbee WP, Michelson EL, Morganroth J. Nonsustained ventricular tachycardia in ambulatory patients: characteristics and associations with sudden cardiac death. *Ann Intern Med* 1980;**92**:741–7.

31 Huang SK, Messer JV, Denes P. Significance of ventricular tachycardia in idiopathic dilated cardiomyopathy: observations in 35 patients. *Am J Cardiol* 1983;**51**:507–11.

32 Franciosa JA, Park M, Levine B. Lack of correlation between exercise capacity and indices of left ventricular performance in heart failure. *Am J Cardiol* 1981;**47**:33–9.

33 Baker BT, Dinh H, Wilen MM, Boyd CM, Franciosa TA. Right but not left ventricular function relates to exercise capacity in chronic left ventricular failure [Abstract]. *Circulation* 1983;**68**(suppl III):III–9.

34 Medical Research Council Working Party on Mild to Moderate Hypertension. Ventricular extrasystoles during thiazide treatment: a sub-study of the MRC Mild Hypertension Trial. *Br Med J* 1983;**287**: 1249–53.

35 Shapiro W. Corrective studies of serum digitalis levels and the arrhythmias of digitalis intoxication. *Am J Cardiol* 1978;**41**:852–9.

36 Harrison CE, Brown AL. Myocardial digoxin-3H content in experimental hypokalaemic cardiomyopathy. *J Lab Clin Med* 1968;**72**:117–28.

37 Steiness E, Olesen KH. Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy. *Br Heart J* 1976;**38**:167–72.

38 Cleland JGF, Dargie HJ, East BW, *et al.* Total body electrolyte composition in heart failure: the effects of captopril. *Eur Heart J* 1985;**6**:681–8.

39 Cleland JGF, Dargie HJ, Robertson I, Robertson JIS, East BW. Total body electrolyte composition in patients with heart failure: a comparison with normal subjects and patients with untreated hypertension *Br Heart J* 1987;**58**:230–8.

40 Gradman AH, Cunningham M, Harbison MA, Berger HJ, Zaret BL. Effects of oral digoxin on ventricular ectopy and its relation to left ventricular function. *Am J Cardiol* 1983;**51**:765–9.

41 Reddy CP, Gettes LS. Use of isoproterenol as an aid to electrical induction of chronic recurrent ventricular tachycardia. *Am J Cardiol* 1979;**44**:705–13.

42 Dargie HJ, Cleland JGF, Leckie BJ, Inglis CG,

East BW, Ford I. Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. *Circulation* 1987;75: IV–98–102.

43 Furberg CD, Yusuf S. Effect of vasodilators on survival in chronic congestive heart failure. *Am J Cardiol* 1985;55:1110–2.

44 Walsh WF, Greenberg BH. Results of long-term vasodilator therapy in patients with refractory congestive heart failure. *Circulation* 1981;64:499–505.

45 Creager MA, Faxon DP, Halperin JL, *et al*. Determinants of clinical response and survival in patients with congestive heart failure treated with captopril. *Am Heart J* 1982;104:1147–54.

46 Sutton R. Haemodynamics of intravenous disopyramide. *J Int Med Res* 1976;4(suppl 1):46–8.

47 Josephson MA, Kaul S, Hopkins J, *et al*. Hemodynamic effects of intravenous flecainide relative to the level of left ventricular function in patients with coronary artery disease. *Am Heart J* 1985;109:41–5.

48 Waagstein F, Hjalmarson Å, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J* 1975;37:1022–36.

49 Taylor SH, Silke B. Haemodynamic effects of beta-blockade in ischaemic heart failure. *Lancet* 1981;ii: 835–7.

50 Ferlinz J, Easthope JL, Aronow WS. Effects of verapamil on myocardial performance in coronary artery disease. *Circulation* 1979;59:313–9.

51 Robinson C, Jackson G, Fisk C, Jewitt D. Haemodynamic effects of atenolol in patients with coronary artery disease. *Br Heart J* 1978;40:22–8.

52 Trobaugh GB, Kudenchuk PJ, Green HL, *et al*. Effect of amiodarone on ventricular function as measured by gated radionuclide angiography. *Am J Cardiol* 1984;54:1263–6.

53 Ellenbogen KA, O'Callaghan WG, Colavita PG, Smith MS, German LD. Cardiac function in patients on chronic amiodarone therapy. *Am Heart J* 1985; 110:376–81.

54 Packer M, Medina N, Yushak M. Hemodynamic and clinical limitations of long-term inotropic therapy with amrinone in patients with severe chronic heart failure. *Circulation* 1984;70:1038–47.

55 Cleland JGF, Dargie HJ, Ball SG, *et al*. Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. *Br Heart J* 1985;54:305–12.

56 Packer M, Medina N, Yushak M, Meller J. Hemodynamic patterns of response during long-term captopril therapy for severe chronic heart failure. *Circulation* 1983;68:803–12.

Br Heart J 1987;58:583–91

Out-of-hospital cardiac arrest in patients without clinically significant coronary artery disease: comparison of clinical, electrophysiological, and survival characteristics with those in similar patients who have clinically significant coronary artery disease

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SUMMARY Fifty nine survivors of out-of-hospital cardiac arrest unassociated with an acute myocardial infarction were referred for intracardiac electrophysiological study. Thirty patients who had no clinically significant coronary artery disease (group 1) were compared with 29 who did (group 2). Ventricular tachycardia or fibrillation was induced in significantly more patients in group 2 than in group 1 (69% *vs* 40%). Median duration of follow up, which was achieved in all patients, was 31 months in group 1 and 14 months in group 2. In group 1, an effective treatment was identified electrophysiologically in seven patients, and none died; an arrhythmia was induced, but no effective treatment was identified in five patients, and one patient died subsequently; an arrhythmia was not induced in 18 patients, 15 of whom were treated empirically with antiarrhythmic drugs, and one died. In group 2, effective treatment was identified electrophysiologically in seven patients and three died (two of pump failure) during follow up. In 13 an arrhythmia was induced but no effective drug was identified, and six died or had a recurrence; in another nine patients without inducible arrhythmias, six subsequently died or had a recurrence. A Cox proportional hazards analysis identified previous myocardial infarction as the only predictor of recurrence.

Patients without coronary artery disease who suffer an out-of-hospital cardiac arrest have a low inducibility rate at electrophysiological study and an excellent prognosis compared with patients who have coronary artery disease. Electrophysiological testing seemed to be of value in predicting the response to antiarrhythmic drugs, but non-inducibility of arrhythmias in patients with coronary artery disease was of no predictive value.

Patients who experience an out-of-hospital cardiac arrest unassociated with acute myocardial infarction have a high recurrence rate.[1,2] Recently, invasive electrophysiological testing has been suggested as a useful method of assessing the efficacy of antiarrhythmic treatment in these patients.[3–5] If the arrhythmia cannot be induced while the patient is on antiarrhythmic drug treatment, long term survival is improved.[4–6] In reported series most patients have had underlying coronary artery disease.[5,7,8] There is

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little information on the role of electrophysiological study and its impact on survival in patients without coronary artery disease who have had an out-of-hospital cardiac arrest. The present study compares the clinical features, the results of electrophysiological study, and survival characteristics in two groups of patients—one with and one without coronary artery disease—who were resuscitated after an out-of-hospital cardiac arrest unassociated with acute myocardial infarction.

Patients and methods

PATIENTS

Fifty nine patients (36 male, 23 female; mean age 52 years, range 5–73) who had survived an out-of-hospital cardiac arrest not associated with an acute myocardial infarction were referred for electrophysiological study between November 1978 and February 1984. In all patients the rhythm at the time of the cardiac arrest was noted (46 had ventricular fibrillation and 13 had ventricular tachycardia), and an associated acute myocardial infarction was excluded by the absence of the typical evolution of electrocardiographic changes or the usual pattern of increase in cardiac enzyme activity. In 55 patients, an adequate estimate of left ventricular ejection fraction was obtained by contrast or radionuclide angiography or cross sectional echocardiography. Forty one patients underwent coronary arteriography.

All patients were followed up either by telephone interview or by direct examination.

PATIENTS WITHOUT CLINICALLY SIGNIFICANT CORONARY ARTERY DISEASE (GROUP 1)

Thirty patients did not have clinically significant coronary artery disease, as shown by angiographically normal vessels or haemodynamically insignificant disease at coronary arteriography (18 patients), a normal maximal treadmill stress test (3 patients), and absence of historical and electrocardiographic evidence of myocardial ischaemia (nine patients). In this last group of nine patients, four were female and three were male who were less than 35 years old (mean, 24 years). The two other patients were men aged 58 and 73; one had the Wolff-Parkinson-White syndrome and the other had clinical features of an idiopathic dilated cardiomyopathy. Table 1 gives the clinical details. In two of the seven patients without overt clinical heart disease, endomyocardial biopsy (right ventricle) showed mild non-specific focal changes of fibrosis without inflammation, the importance of which is uncertain.[9] All seven had normal exercise tolerance, 12 lead electrocardiograms, and left ventricular ejection fractions.

PATIENTS WITH CORONARY ARTERY DISEASE (GROUP 2)

Twenty nine patients had clinical evidence of important coronary artery disease. Criteria for the diagnosis of coronary artery disease included the following: (*a*) important coronary artery disease ($>70\%$ reduction in coronary arterial luminal diameter) at coronary arteriography (23 patients); (*b*) previous history of myocardial infarction (five patients); and (*c*) history of typical exertional angina pectoris (one patient).

ELECTROPHYSIOLOGICAL STUDY

Electrophysiological study was performed within eight weeks of the arrest in 49 patients and between four and 28 months in 10 patients. No patient studied four months or more after cardiac arrest had a recurrence between the time of the arrest and the initial study; some were treated empirically with antiarrhythmic agents. All patients gave informed consent and were studied in the postabsorptive, non-sedated state. All but three had stopped antiarrhythmic drug treatment for at least five half lives before study; the three patients who were on drugs had had recurrent spontaneous arrhythmias since their cardiac arrest that subsequently were apparently controlled by antiarrhythmic medication. Cardiac glycosides were continued in therapeutic doses if clinically indicated. Serum potassium concentration was normal in all patients at the time of study.

One to four standard 7F multielectrode catheter electrodes were inserted percutaneously via the femoral veins or right internal jugular vein and positioned in the right ventricular apex (all patients) and, as clinically indicated, in the high right atrium, His bundle area, and coronary sinus. The pacing protocol used during the electrophysiological study evolved over time. Ventricular stimulation was performed with a Medtronic 5325 stimulator capable of delivering one or two extrastimuli (the first 29 patients) or a Medtronic 2332 stimulator capable of delivering multiple extrastimuli (the last 30 patients) at twice diastolic threshold with a pulse width of 1·9 ms.

Extrastimuli were introduced during sinus rhythm and during two paced rhythms (usually 100 and 150 beats/min), starting with a single stimulus that was used to scan diastole in 20 ms steps until the ventricular effective refractory period was reached. The first stimulus was then advanced by 30 ms and a second stimulus scanned diastole until refractoriness

Table 1 *Clinical details, results of electrophysiological study, treatment, and follow up in patients without coronary artery disease*

Patient	*Cardiac diagnosis*	*Age (yr) and sex*	*LVEF (%)*	*Stimulation protocol*	*Arrhythmia induced*	*Treatment predicted to be successful*	*Follow up (months)*	*Treatment*
1	CM	23, F	42	P, Iso	Sust VT	–	32	Tocainide, mexiletine
2	CM	28, M	24	T	VF	–	20	Amiodarone
3	CM	39, F	27	P	Sust VT	+	63	Tocainide
4	CM	51, F	21	P	Sust VT	+	21	Mexiletine
5	CM	55, F	30	P	–	–	27	Procainamide
6	CM	56, F	24	T, Iso	–	–	5	Amiodarone
7	CM	56, M	11	T	–	–	8	Quinidine
8	CM	63, M	40	P	Sust VT	+	32	Procainamide
9	CM	68, F	39	T, Iso	NSVT	–	5	Procainamide
10	CM	73, F	40	T, Iso	–	–	9	Mexiletine
11	VHD	34, M	28	T	–	–	2 (SD)	Quinidine
12	VHD	38, M	62	T, Iso	–	–	22	β blocker
13	VHD	53, F	50	T, Iso	–	–	3	Amiodarone
14	VHD	56, M	40	P	NSVT	+	27	Mexiletine
15	VHD	63, M	43	P	NSVT	+	59	Quinidine, mexiletine
16	VHD	65, F	27	P	NSVT	–	11 (SD)	Amiodarone
17	HTHD	52, M	41	P	–	–	36	β blocker
18	HTHD	64, M	55	P	Sust VT	–	31	Disopyramide, amiodarone
19	CHD	5, M	—	P	–	–	31	VSD closed
20	CHD	24, M	49	P	Sust VT	+	32	Quinidine
21	MVP	22, F	69	P, Iso	–	–	35	β blocker
22*	Lymphocytic myocarditis	34, M	60	P	–	–	49	β blocker, prednisone
23	WPW	58, M	–	T, Iso	–	–	12	Pacemaker removed, WPW surgery
24	NCHD	17, M	59	P, Iso	–	–	37	β blocker
25	NCHD	23, F	64	T, Iso	–	–	21	Quinidine, β blocker
26*	NCHD	26, F	55	T, Iso	–	–	19 (VT)	Mexiletine, amiodarone
27	NCHD	34, F	62	P	–	–	35	β blocker
28	NCHD	61, F	57	P, Iso	–	–	40	
29*	NCHD	64, M	50	T	NSVT	+	14	β blocker, procainamide
30	NCHD	69, F	72	T, Iso	–	–	1 20	β blocker Amiodarone

*Abnormal endomyocardial biopsy specimen.

CHD, congenital heart disease, CM, cardiomyopathy; HTHD, hypertensive heart disease; Iso, isoprenaline, LVEF, left ventricular ejection fraction, MVP, mitral valve prolapse, NCHD, no overt clinical heart disease, NSVT, non-sustained ventricular tachycardia; P, double extrastimuli; SD, sudden death; Sust VT, sustained ventricular tachycardia; T, triple extrastimuli; VF, ventricular fibrillation; VHD, valvar heart disease, VSD, ventricular septal defect; WPW, Wolff-Parkinson-White syndrome.

was reached. The third stimulus was introduced in a similar fashion.

Incremental ventricular pacing for five beats to 2:1 capture or a paced cycle length of 200 ms was then performed. If no arrhythmia was induced at the right ventricular apex, the catheter electrode was repositioned in the right ventricular outflow tract and the stimulation protocol was repeated. In 19 patients (five in group 1 and 14 in group 2) in whom the above protocol did not induce an arrhythmia, programmed stimulation was repeated during the intravenous infusion of isoprenaline (0·05 mg/kg per min) or stimulation of the left ventricle or both.

DEFINITIONS

Inducible ventricular arrhythmia, more than five beats of ventricular tachycardia or ventricular fibrillation.

Sustained ventricular tachycardia, arrhythmia continuing for >30 s or an intervention (pacing, direct current countershock) was required because of haemodynamic deterioration.

Non-sustained ventricular tachycardia, arrhythmia continuing for more than five beats but for <30 s and without associated haemodynamic deterioration requiring intervention.

Successful antiarrhythmic drug treatment, no more than four return ventricular beats during repeated programmed ventricular stimulation.

Sudden death, death within an hour of the onset of symptoms in a patient free of haemodynamic collapse or myocardial infarction in the preceding 24 hours.

TREATMENT

Patients who had inducible ventricular arrhythmias underwent serial electropharmacological study to define an effective treatment regimen. If an effective antiarrhythmic drug or drug combination was found, the patient was discharged on that regimen. If an effective drug was not found, the patient was given antiarrhythmic drugs that had either increased the difficulty of induction of arrhythmia at electrophysiological study or decreased the frequency and severity of spontaneously occurring arrhythmias during prolonged ambulatory monitoring. The criteria for the latter varied among individual physicians.

Patients in whom an arrhythmia was not inducible at electrophysiological study were treated according to the individual physician's preference.

Eight patients had cardiac operations after evaluation: coronary artery bypass surgery and map-directed endocardial resection in three, coronary bypass surgery alone in three, coronary artery bypass surgery and valve replacement in one, and closure of a ventricular septal defect in one.

STATISTICAL ANALYSIS

Results are expressed as mean (SD). We used logistic regression to assess the possible association of clinical and electrophysiological study variables and the presence or absence of coronary artery disease. Association of the selected variables with time to recurrence or sudden death was evaluated by Cox regression. The assumption of proportional hazards was graphically checked for each covariate; this suggested departures from this assumption for a few covariates.

We then used a stepwise Cox stratified analysis with presence/absence of one or more previous myocardial infarctions as the stratification factor. Within these two strata, no other covariates showed any distinctive departures from the proportional hazards assumption. The same approach was used for overall survival, although here the New York Heart Association functional classification appeared to have a non-proportional hazards structure. After stratification on this covariate (using two strata: functional class 0 or I *vs* class II, III, or IV), a stepwise Cox stratified analysis was then applied to evaluate the possible association of the other covariates with overall survival.

Results

PATIENTS WITHOUT CORONARY ARTERY DISEASE (GROUP 1)

Table 1 gives the clinical, angiographic, and electrophysiological features of the 30 patients in group 1.

Electrophysiological study and follow up

An arrhythmia was induced in 12 of the 30 patients in group 1 (40%); this was sustained ventricular tachycardia or ventricular fibrillation in seven (fig 1). In seven patients successful pharmacological treatment was predicted from the electrophysiological study; none of these died during follow up. In five patients with an inducible arrhythmia, an effective

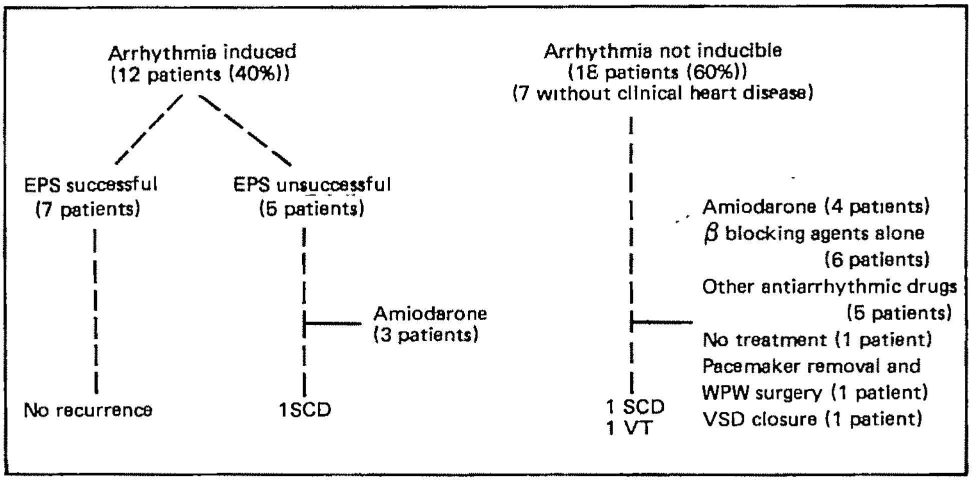

Fig 1 *Results of electrophysiological study (EPS), treatment, and follow up in 30 patients without coronary artery disease (group 1). SCD, sudden cardiac death; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.*

antiarrhythmic drug could not be identified by electrophysiological study; one patient died suddenly during follow up. An arrhythmia could not be induced in 18 patients; 15 were treated with antiarrhythmic drugs prescribed according to physician preference, a malfunctioning pacemaker was removed from one, a ventricular septal defect was closed in one, and one received no treatment. One patient died suddenly during follow up, and ventricular tachycardia recurred in one patient.

PATIENTS WITH CORONARY ARTERY DISEASE (GROUP 2)

Table 2 summarises the clinical, angiographic, and electrophysiological features of the 29 patients in group 2.

Table 2 *Clinical, angiographic, and electrophysiological variables in 29 patients with coronary artery disease*

Variable	*Patients*	
	No	%
Angina class III or IV	3	10
Previous myocardial infarction	23	79
Aneurysm, left ventricle	13	48*
Vessels diseased:		
1	6	26†
2	7	30†
3 or LMCA	10	44†
Arrhythmia inducible:		
None	9	31
NSVT	4	14
Sust VT/VF	16	55
Arrhythmia not inducible after drug treatment	7	24

*Percentage of 27 patients who had imaging of the left ventricle.
†Percentage of 23 patients who had coronary angiography.
LMCA, left main coronary artery; NSVT, non-sustained ventricular tachycardia; Sust VT, sustained ventricular tachycardia; VF, ventricular fibrillation.

Electrophysiological study and follow up

A ventricular arrhythmia was induced in 20 patients (69%), with sustained ventricular tachycardia or ventricular fibrillation being induced in 16 (fig 2). Successful pharmacological treatment was predicted on the basis of the electrophysiological study in seven (35%); two subsequently died in heart failure and one died suddenly (mean follow up 27 months). Thirteen patients continued to have inducible arrhythmias despite treatment; four (31%) died suddenly or had recurrent ventricular arrhythmias (mean follow up 15 months) and two died of pump failure before discharge. In nine patients, ventricular arrhythmias could not be induced; four of these had coronary artery bypass surgery. Four (44%) of the nine patients died suddenly or had recurrent ventricular arrhythmias (one had had coronary artery bypass surgery), and two died of pump failure (one after coronary bypass surgery); the mean follow up was 20 months.

COMPARISON OF PATIENTS IN GROUPS 1 AND 2

Table 3 compares the clinical and electro-

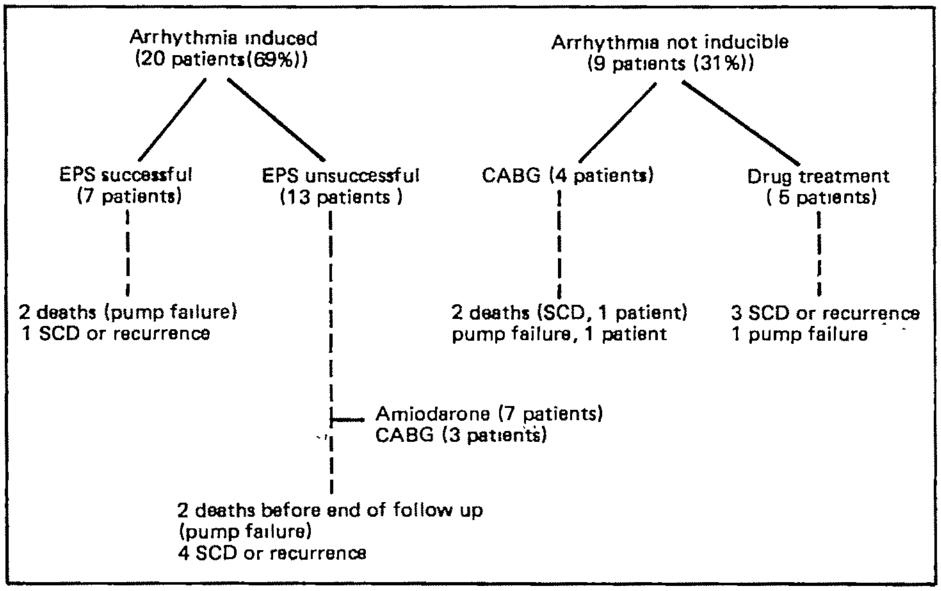

Fig 2 *Results of electrophysiological study (EPS), treatment, and follow up in 29 patients with coronary artery disease (group 2). CABG, coronary artery bypass grafting; SCD, sudden cardiac death.*

Table 3 *Clinical observation and results of electrophysiological study in patients with or without coronary artery disease*

Variable	*Without CAD (group 1)*	*With CAD (group 2)*	*Univariate χ^2 (1 df)*
Clinical·			
Patients (No)	30	29	
Mean (SD) age (yr)	45 (19)	59 (11)	7·9*
Sex (% M)	47	76	5·3†
Smoking (% never)	57	35	1·2
With:			
Hypertension (%)	10	52	12·1*
Heart failure (%)	30	41	<1
Cardiomegaly (%)	37	59	2·9
LV aneurysm (%)	0	34	12·5*
Ejection fraction:			
Mean (SD) (%)	45 (16)	32 (17)	7·3*
No < 35%	8	17	
With previous MI (No)	0	23	39·0*
Electrophysiological:			
Use of triple extrastimuli (No (%))	13 (43)	17 (59)	1·4
LV stimulation or isoprenaline (No (%))	14 (47)	5 (17)	
Inducible arrhythmia (No (%))	12 (40)	20 (69)	6·2†
Sustained (No)	7	16	
Non-sustained (No)	5	4	
Other EPS abnormalities (No (%))	12 (40)	18 (62)	2·9
Median time from arrest to EPS (days)	18	18	
(25th–75th percentiles) (days)	(10, 61)	(9, 36)	1·5
Drug success based on EPS			9·6*

CAD, coronary artery disease; EPS, electrophysiological study; LV, left ventricular; MI, myocardial infarction; NS, not significant.
*Association with presence/absence of CAD ($p < 0.01$).
†Association with presence/absence of CAD ($p < 0.05$).

physiological variables in patients with and without coronary artery disease. The patients without coronary artery disease were younger, were more evenly distributed between the sexes, and had a lower frequency for hypertension. Logistic regression analysis indicated that previous myocardial infarction and hypertension were the features most strongly associated with coronary artery disease. No other variables were independently associated with coronary artery disease. The frequencies of clinically apparent heart failure and radiologically apparent cardiomegaly were similar in both groups, but left ventricular ejection fraction was lower in patients with coronary artery disease. There were no differences in stimulation protocols between groups, but more patients without coronary artery disease had left ventricular stimulation or isoprenaline infusion as part of the protocol. This probably reflects the greater ease of induction of arrhythmia by standard stimulation protocols in patients with coronary artery disease. Median follow up was 13·9 months in the patients with coronary artery disease and 31·2 months in those without coronary artery disease.

In seven patients without coronary artery disease and seven with coronary artery disease, effective treatment was identified by electrophysiological study. During follow up of these patients, none without coronary artery disease died or had recurrence of arrhythmia, but there were four deaths or recurrences in the seven patients with coronary artery disease (pump failure in two).

Amiodarone was given to 14 patients (seven without and seven with coronary artery disease). During follow up, two patients died suddenly and one had a recurrence (total recurrence rate 21%).

SURVIVAL

Figure 3 shows the estimated survival (Kaplan-Meier) for patients with and without coronary artery

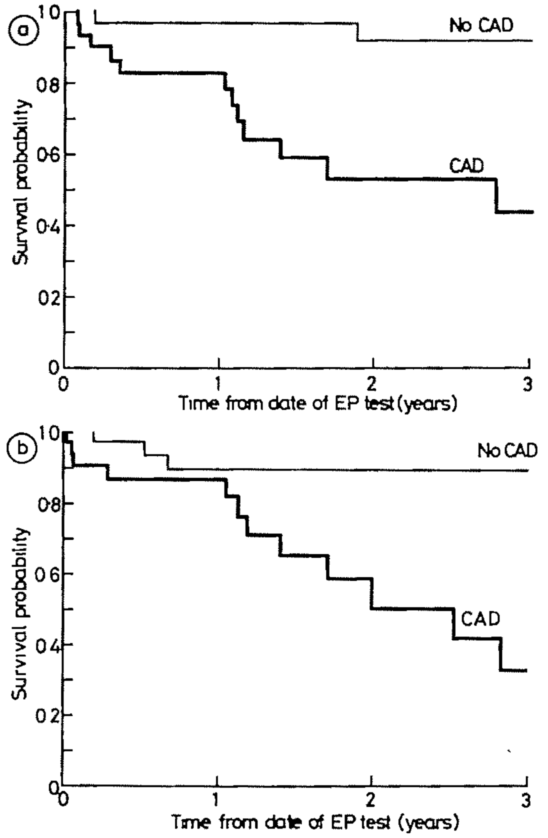

Fig 3 *Cumulative survival of patients stratified according to the presence or absence of clinically significant coronary artery disease. (a) Including all causes of death; (b) survival without sudden cardiac death or recurrence of life threatening ventricular arrhythmia. EP, electrophysiological.*

disease. In group 1, one patient had a recurrence of arrhythmia and survived and two died suddenly. In only one of these three patients was arrhythmia inducible at electrophysiological study (patient 16); however, electrophysiological study did not identify successful drug treatment. In group 2, there were nine sudden cardiac deaths or recurrences of a life threatening arrhythmia. Six patients in group 2 died of myocardial pump failure and three of them had recurrent ventricular tachycardia before death. Thus the total cardiac mortality rate of patients was 7% in group 1 and 41% in group 2. If all cardiac deaths and recurrences of life threatening arrhythmias are included, 10% of those in group 1 died or had a recurrence compared with 52% in group 2.

ANALYSIS BY THE COX MODEL

For analyses by the Cox model the presence or absence of previous myocardial infarction was used as a stratifying factor when the end point was recurrence or sudden cardiac death and New York Heart Association functional class was used when overall survival was the end point. Univariate analysis of *time to recurrence or sudden death* showed statistically significant associations with only previous myocardial infarction, left ventricular aneurysm, coronary artery disease, and ejection fraction. When previous myocardial infarction was used as a stratification factor there was no significant association with other variables. The analysis of *overall survival* indicated that only previous myocardial infarction, coronary artery disease, functional class, and cardiomegaly were univariately associated with survival. The analysis stratified by functional class showed an association with previous myocardial infarction, but when this too was used as a stratifying factor no other factors showed a significant association.

Discussion

We have shown that patients who survive a cardiac arrest unassociated with an acute myocardial infarction and who do not have underlying coronary artery disease have lower rates of cardiac mortality and arrhythmia recurrence than do similar patients who have documented coronary artery disease (10% *vs* 52%); however, this lower mortality is not statistically significant after adjustment for a history of previous myocardial infarction. The strong association between previous myocardial infarction and sudden cardiac death in patients with coronary artery disease is expected and is entirely consonant with pathological and epidemiological data. There were no clinical or haemodynamic predictors of death or recurrence of arrhythmia in the group without coronary artery disease. Of the three patients who had recurrences, two had valvar heart disease (one in New York Heart Association functional class II and one in class III; left ventricular ejection fractions were 27% and 28%, respectively). There were five other patients in the group with similar or lower ejection fractions who remained event free.

Follow up information on survivors of out-of-hospital cardiac arrest who specifically did not have overt coronary artery disease is available only in one previous study.[4] In that study, 13 of 33 patients with a spontaneous cardiac arrest caused by ventricular fibrillation or ventricular tachycardia did not have coronary artery disease. During a mean follow up of survivors for 29 months, five patients (three with primary electrical heart disease and two with cardiomyopathy) died suddenly or had a recurrence, giving a cardiac mortality and recurrence rate of 38%. In the present series the rate was 10%. Details of left ventricular function and the success of electrophysiological study in the patients without coronary artery disease were not given. The reasons for the difference in mortality and recurrence rate between this study and ours are not apparent, but it may reflect differences in sample size, composition, and treatment. Most importantly, the difference may reflect selection bias, perhaps related to variations in hospital referral practices.

The frequency with which ventricular arrhythmias can be induced in patients without coronary artery disease was significantly lower than that in patients with coronary artery disease (40% *vs* 69%); again, these differences are not significant when adjusted for a history of previous myocardial infarction. Skale *et al* recently reported the results of electrophysiological study in 62 survivors of out-of-hospital cardiac arrest; of these, 35% had coronary artery disease.[8] As in our series, the inducibility rate was higher in those with coronary artery disease (85% *vs* 60%). Skale *et al*, however, did not present a follow up categorised according to the presence or absence of coronary artery disease.

The overall mortality (including sudden and non-sudden deaths) and recurrence for our total group of patients was 31%, which resembles the 13–39% reported in previous studies.[4–6] The striking feature of the present study is the poor outcome in patients with coronary artery disease; 15 (52%) of 29 patients with coronary artery disease died or had recurrent arrhythmias. Myocardial pump failure was the cause of 40% of the deaths and, given the overall poor left ventricular function in this group (mean left ventricular ejection fraction 32%), the presence of severe myocardial damage before the cardiac arrest is the most likely explanation for this observation.

Studies of outcome in patients who have survived an out-of-hospital cardiac arrest demonstrated an overall mortality and recurrence rate of 32% at one year and 47% at two years.[1] A significant proportion (27%) of these deaths were not sudden but were caused by myocardial pump failure. Studies suggest that treatment guided by electrophysiological study reduces overall mortality and recurrence rates, but still a significant number of patients died despite this procedure being followed.[4-6] Indeed, it would be unrealistic to think that electrophysiological study alone in these patients, many of whom have multivessel coronary artery disease or severely compromised left ventricular function, could define optimal treatment for all.[4 6 10] The electrophysiological study may not reproduce transient dynamic events—for example, ischaemia or an electrolyte disturbance—that may have precipitated the initial cardiac arrest.[11-13] Clearly, other forms of treatment must be explored in these high risk patients.

LIMITATIONS

Like similar previous studies, the present one is retrospective and lacks controls. Therefore, our conclusions must be tentative. Furthermore, although it seems logical to compare the subgroup with coronary artery disease with the subgroup without, the influence of selection bias on comparisons of these groups and the various aetiologies within the group without coronary artery disease cannot be determined. Programmed ventricular stimulation was not performed in all patients in the present study after the start of "empiric" antiarrhythmic treatment. This usually occurred in the setting of a negative electrophysiological study at baseline and the perceived need of the attending physician to offer some treatment to a patient who had suffered a cardiac arrest. Thus an arrhythmogenic effect may have been missed in some patients. Nor was programmed ventricular stimulation performed in patients on amiodarone. The recent information[14 15] that suggests that programmed ventricular stimulation in patients on amiodarone treatment is valuable was not available during this study. Finally, the automatic implantable defibrillator was not available to us during the early part of this study; undoubtedly, this device would now be used and may have improved the survival of patients after an out-of-hospital cardiac arrest in whom inducible arrhythmias were not responsive to antiarrhythmic drug treatment and who were not suitable candidates for electrosurgery.

CONCLUSIONS

Among patients who suffer an out-of-hospital cardiac arrest without an associated acute myocardial infarction those without coronary artery disease seem to have a better prognosis than those who have coronary artery disease. The usefulness of electrophysiological testing in these patients is limited by the low rate of arrhythmia inducibility and the small number of patients who respond to specific antiarrhythmic treatment. Those patients who responded to specific drug treatment, however, did well during the 23 month follow up. Electrophysiological studies therefore seem to be useful in identifying a small number of patients who have an excellent long term prognosis. This emphasises the fact that patients who survive an out-of-hospital cardiac arrest unassociated with an acute myocardial infarction should be comprehensively investigated to define the presence, nature, and severity of the underlying heart disease and that electrophysiological testing has a limited but, none the less, useful role in defining treatment and prognosis.

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References

1 Cobb LA, Baum RS, Alvarez H III, Schaffer WA. Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up. *Circulation* 1975; 52(suppl 3):223–8.

2 Liberthson RR, Nagel EL, Hirschman JC, Nussenfeld SR. Prehospital ventricular defibrillation: prognosis and follow-up course. *N Engl J Med* 1974;**291**: 317–21.

3 Ruskin JN, DiMarco JP, Garan H. Out-of-hospital cardiac arrest: electrophysiologic observations and selection of long-term antiarrhythmic therapy. *N Engl J Med* 1980;**303**:607–13.

4 Benditt DG, Benson DW Jr, Klein GJ, Pritzker MR, Kriett JM, Anderson RW. Prevention of recurrent sudden cardiac arrest: role of provocative electropharmacologic testing. *J Am Coll Cardiol* 1983;**2**: 418–25.

5 Roy D, Waxman HL, Kienzle MG, Buxton AE, Marchlinski PE, Josephson ME. Clinical characteristics and long-term follow-up in 119 survivors of cardiac arrest: relation to inducibility at electrophysiologic testing. *Am J Cardiol* 1983;**52**:969–74.

6 Ruskin JN, Garan H, DiMarco JP, Kelly E. Electrophysiologic testing in survivors of prehospital cardiac arrest: therapy and long-term follow-up [Abstract]. *Am J Cardiol* 1982;**49**:958.

7 Morady F, Scheinman MM, Hess DS, Sung RJ, Shen E, Shapiro W. Electrophysiologic testing in the management of survivors of out-of-hospital cardiac arrest. *Am J Cardiol* 1983;**51**.85–9.

8 Skale BT, Miles WM, Heger JJ, Zipes DP, Prystowsky EN. Survivors of cardiac arrest: prevention of recurrence by drug therapy as predicted by electro-

physiologic testing or electrocardiographic monitoring. *Am J Cardiol* 1986;57:113–9.

9 Sugrue DD, Holmes DR Jr, Gersh BJ, *et al.* Cardiac histologic findings in patients with life-threatening ventricular arrhythmias of unknown origin. *J Am Coll Cardiol* 1984;4:952–7.

10 Morady F, DiCarlo L, Winston S, Davis JC, Scheinman MM. Clinical features and prognosis of patients with out of hospital cardiac arrest and a normal electrophysiologic study. *J Am Coll Cardiol* 1984;4:39–44.

11 Deanfield JE, Maseri A, Selwyn AP, *et al.* Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. *Lancet* 1983;ii:753–8.

12 Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta$_2$-receptor stimulation by circulating epinephrine. *N Engl J Med* 1983;309:1414–9.

13 Thompson RG, Cobb LA. Hypokalemia after resuscitation from out-of-hospital ventricular fibrillation. *JAMA* 1982;248:2860–3.

14 Naccarelli GV, Fineberg NS, Zipes DP, Heger JJ, Duncan G, Prystowsky EN. Amiodarone: risk factors for recurrence of symptomatic ventricular tachycardia identified at electrophysiologic study. *J Am Coll Cardiol* 1985;6:814–21.

15 McGovern B, Garan H, Malacoff RF, *et al.* Long-term clinical outcome of ventricular tachycardia or fibrillation treated with amiodarone. *Am J Cardiol* 1984;53:1558–63.

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Impaired vagal heart rate control in coronary artery disease

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SUMMARY Heart rate variation in deep breathing, a sensitive non-invasive measure of cardiac parasympathetic activity, was measured in 63 patients with coronary artery disease, in 22 patients with atypical chest pain, and in 20 healthy symptom free volunteers. There was significantly less heart rate variation in deep breathing in the patients with coronary artery disease than in the healthy subjects. Twenty patients (32%) with coronary artery disease had lower than normal variation in heart rate. The patients with chest pain showed an intermediate heart rate response to deep breathing. Sinus arrhythmia in the patients with coronary artery disease was not related to the functional class, medication, number or location of narrowed vessels, or to the left ventricular ejection fraction, and end diastolic pressure.

These results suggest that impairment of the parasympathetic nervous function is common in coronary artery disease.

The harmful effects of increased sympathetic activity after myocardial infarction are well established and the beneficial effects of sympathetic blockade in reducing mortality in high-risk patients have been recognised.[1-3] Recently, attention has also been directed toward the electrophysiological effects of the parasympathetic nervous system. Reduced vagal activity is associated with an increased frequency of cardiac death,[4-6] and parasympathetic blockade may precipitate ventricular arrhythmias including ventricular fibrillation.[7 8]

The majority of patients with acute myocardial infarction show evidence of autonomic disturbances during the acute stage of the attack.[9 10] The suggestion that there is dysfunction of the parasympathetic nervous system in stable coronary artery disease[11 12] and after myocardial infarction[13 14] is, however, more controversial and based on relatively small series of patients. We have evaluated parasympathetic nervous function in coronary artery disease by standard non-invasive cardiovascular tests and have related our findings to the clinical and angiographic features of coronary artery disease.

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Patients and methods

PATIENTS

We studied 63 patients (57 men, six women) with coronary artery disease. They were consecutive patients referred for elective cardiac catheterisation in our hospital and fulfilled the following inclusion criteria: age <60 years; no valvar heart disease, hypertension, manifest heart failure, or atrial fibrillation; not on antiarrhythmic medication or other medication known to have anticholinergic activity; and no diabetes mellitus or uraemia.

The mean age of the patients was 50 years (range 33–59) and 36 patients had had a myocardial infarction (eight anterior, 15 inferior, and 13 non-Q wave). None was in the acute stage of the attack. Seven patients were in New York Heart Association class IV, 36 patients in class III, and 20 patients in class II. Their medication included β blockers in 42 cases (67%), calcium antagonists in 29 cases (46%), nitrates in 47 cases (75%), digitalis in 11 cases (18%), and diuretics in nine cases (14%).

The control group of 20 healthy subjects (10 men, 10 women) of the same age group (mean age 46, range 36–55 years) was recruited among the employees of a nearby pulp mill and among hospital staff. None was taking any medication known to affect autonomic nervous function. They were healthy as shown by history, physical examination, chest x rays, echocardiogram, and exercise electrocardiogram.

A group of 22 patients (10 men, 12 women) with atypical chest pain was also assessed to evaluate the potential effects of long term antianginal medication and reduced physical activity on the autonomic control of heart rate. They were consecutive patients catheterised because of disabling symptoms and fulfilling the inclusion criteria. Their mean age was 47 years (range 35–59 years) and all had normal electrocardiograms, chest x rays, echocardiograms, left ventricular cineangiograms, and coronary angiograms. Their medication included β blockers and nitrates in 14 cases (64%), calcium antagonists in 10 cases (45%), diuretics in three cases (13%), and digitalis in one case (5%). Informed consent was obtained from all the subjects.

CARDIAC CATHETERISATION

All patients underwent left-sided cardiac catheterisation, including selective coronary arteriography performed by the Judkins' technique. Biplane left ventricular cineangiography was performed in the 45° right anterior oblique position. The angiographic findings were interpreted by two independent observers who were unaware of the tests of the autonomic nervous function. A stenosis causing reduction of $>50\%$ in the luminal diameter of a coronary artery was regarded as an important lesion. Left ventricular pressures were recorded with a Statham 2351a transducer, and a data acquisition system (Hewlett-Packard 5400B) was used for analysis of pressure.

TESTS OF AUTONOMIC NERVOUS FUNCTION

The tests of autonomic nervous function were performed by specially trained nurses in the cardiovascular laboratory on patients in a postabsorptive state during the morning of the day before cardiac catheterisation. The patients were on their regular medication. Smoking and coffee drinking were not allowed in the morning before the tests. The heart rate was recorded with an instantaneous beat to beat rate recorder (Hewlett-Packard 8812 A rate computer). After a demonstration of the procedures and 10 minutes of supine rest the patients were asked to take six deep breaths. The depth of respiration is not critical as long as it is more than 40% of the vital capacity, but the rate of breathing is important and was standardised at six per minute.[15 16] The difference between the maximum and minimum heart rate during each breath was measured and the mean was taken as the heart rate variation during deep breathing (fig 1).

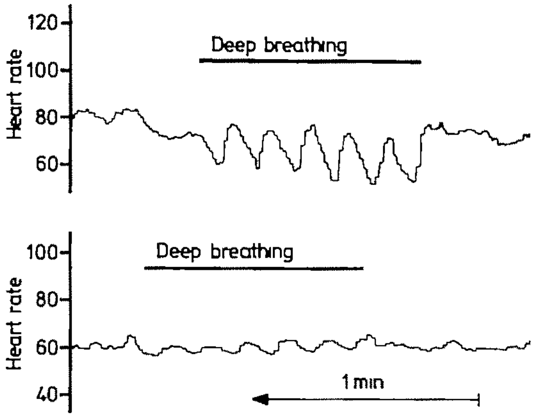

Fig 1 *Normal heart rate variation during deep breathing in a healthy subject (above) and a blunted heart rate variation in a patient with coronary artery disease (below).*

About 1–2 minutes after forced breathing the patients stood up quickly. The shortest RR interval at around the fifteenth beat after standing and the longest RR interval at around the thirtieth beat after standing were measured to show the response of the heart rate to standing (the 30:15 ratio).[16] Generally accepted normal values were used to evaluate these tests.[16]

Supine heart rate was determined as the mean rate over a 30 s period before standing up. The mean heart rate of the last 30 s during the two minutes' standing was taken as the standing heart rate. Blood pressure was measured with a sphygmomanometer while the patient was lying down and after 30–60 s of standing.

The reproducibility of the tests was assessed by examining 11 subjects (three with coronary artery disease) twice at an interval of at least two days. The mean (SD) difference in heart rate variation during deep breathing between test 1 and test 2 was 0 (4) (SD) beats/min (NS). The corresponding difference in the 30:15 ratio was +0·05 (0·19) (NS).

To assess ventricular parasympathetic reflexes,[17] we measured the degree of bradycardia induced by coronary arteriography—that is the shortest RR interval at the beginning of each coronary injection and the longest RR interval at around the end of each injection—and the induced maximum lengthening was expressed as a percentage. Only cases in which Urografin 76 was used as the contrast medium and who received no atropine as premedication were included in the analysis.

To assess the effects of cardiovascular medication on the tests of autonomic nervous function the drugs were gradually withdrawn at least two days (digitalis one week) before the tests in 12 patients with stable

Table 1 *Heart rate and blood pressure changes evoked by standing up and the catheterisation data in the study groups (mean (SD))*

Variable	*CAD patients (n = 63)*	*Controls (n = 20)*	*Patients with chest pain (n = 22)*
Heart rate, supine (beats/min)	67 (12)	69 (11)	73 (11)
Heart rate, standing (beats/min)	82 (14)‡	83 (15)	93 (14)
The 30:15 ratio	1·21 (0·15)	1·27 (0·21)	1·24 (0·13)
Blood pressure, supine (mm Hg)			
Systolic	130 (18)	126 (14)	128 (15)
Diastolic	82 (10)	82 (11)	80 (13)
Blood pressure, standing (mm Hg).			
Systolic	122 (17)	121 (18)	118 (17)
Diastolic	85 (11)	80 (14)	85 (12)
LV end diastolic pressure (mm Hg)	12·9 (5·0)	—	14·7 (6·0)
LV end diastolic volume (ml)*	160 (34)§	—	126 (28)
LV ejection fraction (%)*	59 (10)§	—	70 (7)
RR interval change in response to coronary arteriography (%)†	66 (67)	—	50 (42)

CAD, coronary artery disease, LV, left ventricular. *Data on 35 patients with CAD and 12 patients with chest pain. †Data on 35 patients with CAD and nine with chest pain. Difference *vs* patients with chest pain ‡ $p < 0.05$, § $p < 0.01$.

coronary artery disease and the tests were repeated one day after the treatment was resumed (β blockers in nine patients, nitrates in nine patients, calcium antagonists in seven patients, and digitalis in four patients).

STATISTICAL ANALYSIS

Differences between the three groups were evaluated by analysis of variance followed by the Bonferroni modification of t test. A paired or unpaired t test was used when appropriate and Fisher's test was used to evaluate the differences in frequencies. Standard formulas were used to calculate the linear correlations.

Results

CATHETERISATION DATA

Table 1 shows the catheterisation data in the patients. Five (8%) of the patients with coronary artery disease had an important stenosis of left main coronary artery; 34 patients (54%) had three vessel disease, 11 (17%) two vessel disease, and 13 (20%) one vessel disease.

PARASYMPATHETIC NERVOUS FUNCTION

There was less variation in heart rate during deep breathing in patients with coronary artery disease than in healthy subjects (difference between means 5, 95% confidence interval one to 10 beats/min), but not in patients with chest pain (fig 2). In the subgroup analysis of the patients, 40% of those with local akinesia or dyskinesia, 26% of the remaining patients with coronary artery disease, and 18% of the patients with chest pain had abnormal (≤10 beats/min) heart rate variation in deep breathing. One healthy subject also had a heart rate variation just below the lower limit of normal (fig 2).

The number or location of affected vessels did not significantly affect the variation in heart rate during deep breathing. Nor was the variation related to New York Heart Association class, left ventricular ejection fraction, or end diastolic pressure in the patients with coronary artery disease. The medication taken by patients with abnormal heart rate vari-

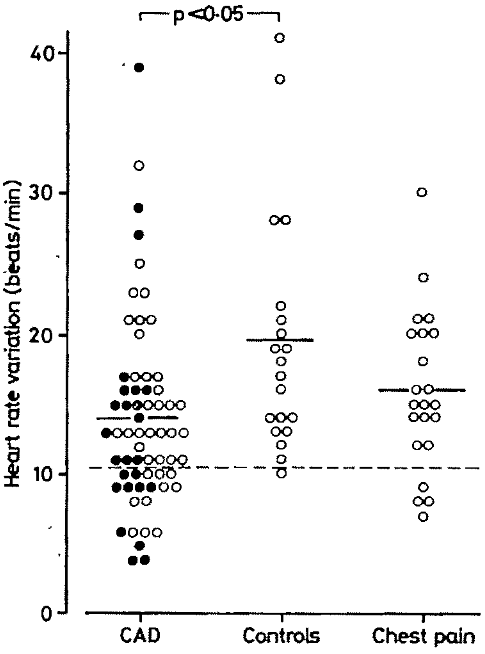

Fig 2 *Heart rate variation in deep breathing in patients with coronary disease (CAD), healthy subjects, and patients with chest pain. Patients with transmural myocardial infarction (●). Broken line shows lower limit of normal.*

Table 2 *Clinical and catheterisation data on patients with coronary artery disease who had normal or abnormal heart rate variation during deep breathing (mean (SD))*

Variable	*Normal heart rate variation (n = 43)*	*Abnormal heart rate variation (n = 20)*
Age	50 (6)	51 (5)
Mean NYHA class	2·8	2·9
Treatment:		
β Blockers	29 (67%)	13 (65%)
Calcium antagonists	23 (53%)	6 (30%)
Nitrates	30 (70%)	17 (85%)
Digitalis	9 (21%)	2 (10%)
Diuretics	8 (19%)	1 (5%)
Heart rate, supine (beats/min)	67 (10)	66 (16)
Heart rate, standing (beats/min)	83 (12)	79 (17)
The 30:15 ratio	1·23 (0·16)	1·15 (0·11)*
Blood pressure, supine (mm Hg).		
Systolic	131 (20)	126 (13)
Diastolic	82 (10)	81 (10)
Blood pressure, standing (mm Hg).		
Systolic	126 (17)	115 (17)*
Diastolic	86 (10)	83 (12)
Location of coronary stenosis.		
Left main coronary artery	4 (9%)	1 (5%)
Left anterior descending branch	38 (88%)	19 (95%)
Circumflex branch	32 (74%)	13 (65%)
Right coronary artery	32 (74%)	13 (65%)
LV end diastolic pressure (mm Hg)	12·8 (5·9)	13·3 (5·3)
LV end diastolic volume (ml)	158 (37)	166 (26)
LV ejection fraction (%)	60 (10)	57 (11)
RR interval change in response to coronary arteriography (%)	71 (72)	53 (48)

NYHA, New York Heart Association; LV, left ventricular. Difference between the groups: *$p < 0·05$

ation did not differ significantly from that of the patients with normal heart rate variation (table 2) or of the patients with chest pain. Heart rate variation in deep breathing was not significantly related to age in the patients with coronary artery disease ($r = -0·05$), but tended to diminish with age in the other subjects ($r = -0·29$, $n = 42$).

Changes in heart rate evoked by standing up (the 30:15 ratio) as well as supine and standing blood pressure were not significantly different in the three groups (table 1). In the subgroup analysis of patients with coronary artery disease, the standing systolic blood pressure and the 30:15 ratio of the patients with abnormal heart rate variation were, however, lower than those in the patients with normal heart rate variation ($p < 0·05$) (table 2).

The mean (SD) heart rate variation in deep breathing was similar after withdrawal and reinstitution of the cardiovascular medication (13·8 (7·4) and 11·6 (7·1) beats/min, respectively, NS) in the 12 patients in which it is evaluated.

The bradycardia caused by coronary arteriography was not significantly different in patients with coronary artery disease and those with chest pain.

Discussion

The variation in heart rate induced by deep breathing is the single most sensitive and reproducible non-invasive test of cardiac parasympathetic activity.[18,19] It correlates closely with invasive measurement of parasympathetic heart rate control—for example, baroreflex sensitivity.[18] Several physiological mechanisms contribute to respiratory sinus arrhythmia. These include both reflex mechanisms (pulmonary stretch receptors, baroreceptors, Bainbridge reflex) and the direct interaction of the respiratory and cardiovascular medullary centres.[20] The fact that vagotomy and atropine abolish respiratory sinus arrhythmia and that recorded vagal efferent activity closely predicts the magnitude of heart rate variation shows that parasympathetic efferents are mainly responsible for mediating these effects.[20,21] Changes in heart rate induced by standing up also reflect mainly parasympathetic heart rate control, but are not so useful because they are less sensitive and have a wider range of normal responses, especially in older people.[22,23]

Our study suggests that cardiac vagal efferent activity is depressed in coronary artery disease. Earlier studies of autonomic nervous function in coronary artery disease have given somewhat divergent results. Ryan *et al* found impaired parasympathetic response to facial immersion, but normal sympathetic pressor responses in 27 patients three months after myocardial infarction.[13] On the other hand, Bennett *et al* found impaired sympathetic responses in a group of 18 asymptomatic patients studied at least one year after myocardial infarction.[14] The difference in parasympathetic responses did not reach statistical significance, although the values were comparable to those in the present study. The heart rate response to the Valsalva manoeuvre has been reported to be abnormally low in patients with coronary artery disease,[11] although they may have an exaggerated heart rate response to carotid sinus massage.[12] The apparent discrepancies may result from the fact that various tests reflect different aspects of autonomic nervous function.

We cannot explain the impairment of vagal control of heart rate in coronary artery disease. Heart rate variation tends to decline with age in healthy subjects,[23,24] but heart rate variation in deep breathing was not affected by age in patients with coronary artery disease, so it seems that minor differences in age between the groups were not a crucial factor. Earlier observations suggest that medication was unlikely to have had any major impact on our findings.[6,14,25] This view is supported by the findings that the withdrawal of medication did not significantly alter the heart rate variation and that patients with abnormal and normal heart rate variation in deep breathing were on similar medication.

The level of physical activity may affect the parasympathetic tone and reflex heart rate control.[26] Interestingly, the patients with chest pain also had slightly diminished heart rate responses to deep breathing, which might suggest that reduced physical activity caused by disabling symptoms may contribute to the blunting of heart rate variation. The severity of symptoms did not, however, correlate with the heart rate variation in deep breathing.

Earlier experimental studies have shown that transmural infarction can interrupt both the afferent and efferent limbs of the autonomic innervation of the myocardium apical to the infarction.[27] Heart rate variation in deep breathing or the degree of bradycardia caused by coronary arteriography, however, were not significantly reduced in patients with transmural myocardial infarction compared with other patients with coronary artery disease. Nor was heart rate variation in deep breathing related to the location or number of diseased vessels or to left ventricular function. So it seems that reduced vagal efferent activity in coronary artery disease cannot be predicted by any specific feature of the disease.

The role of the parasympathetic nervous system in protecting the heart against serious ventricular arrhythmias and sudden death has recently attracted attention. The interaction of the parasympathetic nervous system with the sympathetic nervous system can buffer the deleterious effect of sympathetic storm on the threshold for ventricular fibrillation.[28,29] Experimental studies have shown that dogs with a healed myocardial infarction and reduced levels of cardiac vagal activity are liable to exercise-induced ventricular fibrillation and that subsequent increases in vagal activity protect against ventricular fibrillation.[26] In accordance with this, reduced respiration-related variation in heart rate is associated with an increased frequency of cardiac death both in middle aged men[5] and after myocardial infarction.[6,30] These studies suggest that a diminished heart rate variation in deep breathing, a simple bedside measure of cardiac vagal activity, might identify a subpopulation of patients with coronary artery disease who are at an increased risk of sudden death. It is not yet known whether interventions known to augment the vagal activity—for example pharmacological ones,[31] and exercise programmes, or on the other hand blocking of sympathetic activity, might be of particular value in this group of patients.

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References

1 Han J, Garcia de Jalon P, Moe GK. Adrenergic effects on ventricular vulnerability. *Circ Res* 1964;14:516–24.

2 Wilhelmsson C, Vedin JA, Wilhelmsen L, Tibblin G, Werko L. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* 1974;ii:1157–60.

3 The Norwegian multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;304:801–7.

4 Billman GE, Schwartz PJ, Stone HL. Baroreceptor reflex control of heart rate: a predictor of sudden cardiac death. *Circulation* 1982;66:874–80.

5 Hinkle LE, Carver ST, Plakun A. Slow heart rates and increased risk of cardiac death in middle-aged men. *Arch Intern Med* 1972;129:732–48.

6 Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256–62.

7 Massumi RA, Mason DT, Amsterdam EA, *et al*. Ventricular fibrillation and tachycardia after intravenous atropine for treatment of bradycardias. *N Engl J Med* 1972;287:336–8.

8 Schwartz PJ, Billman GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. *Circulation* 1984;69:790–800.

9 Kirby BJ. Circulatory reflexes in myocardial infarction. *Br Heart J* 1977;39:168–72.

10 Imaizumi T, Takeshita A, Makino N, Ashihara T, Yamamoto K, Nakamura M. Impaired baroreflex

control of vascular resistance and heart rate in acute myocardial infarction. *Br Heart J* 1984;**52**:418–21.

11 Tristani FE, Kamper DG, McDermott DJ, Peters BJ, Smith JJ. Alterations of postural and Valsalva responses in coronary heart disease. *Am J Physiol* 1977;**233**:H694–9.

12 Brown KA, Maloney JD, Smith H, Hartzler GO, Ilstrup DM. Carotid sinus reflex in patients undergoing coronary angiography: relationship of degree and location of coronary artery disease to response to carotid-sinus massage. *Circulation* 1980;**62**:697–703.

13 Ryan C, Hollenberg M, Harvey DB, Gwynn R. Impaired parasympathetic responses in patients after myocardial infarction. *Am J Cardiol* 1976;**37**:1013–8.

14 Bennett T, Wilcox RG, Hampton JR. Cardiovascular reflexes in patients after myocardial infarction. Effect of long-term treatment with beta-adrenoreceptor antagonists. *Br Heart J* 1980;**44**:265–70.

15 Bennett T, Farquhar IK, Hosking DJ, Hampton JR. Assessment of methods for estimating autonomic nervous control of the heart in patients with diabetes mellitus. *Diabetes* 1978;**27**:1167–74.

16 Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 1982;**285**:916–8.

17 Carson RP, Lazzara R. Hemodynamic responses initiated by coronary stretch receptors with special reference to coronary arteriography. *Am J Cardiol* 1970;**25**:571–8.

18 Watkins PJ, Mackay JD. Cardiac denervation in diabetic neuropathy. *Ann Intern Med* 1980;**92**:304–7.

19 Ewing DJ, Borsey DQ, Bellavere F, Clarke BF. Cardiac autonomic neuropathy in diabetes: comparison of measures of R-R interval variation. *Diabetologia* 1981;**21**:18–24.

20 Katona PG, Jih F. Respiratory sinus arrhythmia: non-invasive measure of parasympathetic cardiac control. *J Appl Physiol* 1975;**39**:801–5.

21 Katona PG, Poitras JW, Barnett GO, Terry BS. Cardiac vagal efferent activity and heart period in the carotid sinus reflex. *Am J Physiol* 1970;**218**:1030–7.

22 Dyrberg T, Benn J, Christiansen JS, Hilsted J, Nerup J. Prevalence of diabetic autonomic neuropathy measured by simple bedside tests. *Diabetologia* 1981;**20**:190–4.

23 Pfeifer MA, Weinberg CR, Cook D, Best JD, Reenan A, Halter JB. Differential changes of autonomic nervous system function with age in man. *Am J Med* 1983;**75**.249–58.

24 O'Brien IAD, O'Hare P, Corrall RJM. Heart rate variability in healthy subjects: effect of age and the derivation of normal ranges for tests of autonomic function. *Br Heart J* 1986;**55**:348–54.

25 Pfeifer MA, Cook D, Brodsky J, *et al*. Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man. *Diabetes* 1982;**31**:339–45.

26 Billman GE, Schwartz PJ, Stone HL. The effects of daily exercise on susceptibility to sudden cardiac death. *Circulation* 1984;**69**:1182–9.

27 Barber MJ, Mueller TM, Davies BG, Gill RM, Zipes DP. Interruption of sympathetic and vagal-mediated afferent responses by transmural myocardial infarction. *Circulation* 1985;**72**:623–31.

28 Muscholl E. Peripheral muscarinic control of norepinephrine release in the cardiovascular system. *Am J Physiol* 1980;**239**:H713–20.

29 Hohnloser SH, Verrier RL, Lown B. Effects of adrenergic and muscarinic receptor stimulation on serum potassium concentrations and myocardial electrical stability. *Cardiovasc Res* 1986;**20**:891–6.

30 Wolf MM, Varigos GA, Hunt D, Sloman JG. Sinus arrhythmia in acute myocardial infarction. *Med J Aust* 1978;**ii**:52–3.

31 Dibner-Dunlap ME, Eckberg DL, Magid NM, Cintron-Trevino NM. The long-term increase of baseline and reflexly augmented levels of human vagal-cardiac nervous activity induced by scopolamine. *Circulation* 1985;**71**:797–804.

Br Heart J 1987;58:598–607

Chronic sinoatrial disorder (sick sinus syndrome): a possible result of cardiac ischaemia

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SUMMARY Postmortem angiography was used to examine the blood vessels supplying the sinoatrial node in 25 subjects with chronic sinoatrial disorder (group 1). The results were compared with similar studies in 54 subjects who died of heart block and in whom sinus node function was normal (group 2). Although no significant lesion obstructing the blood flow to the sinus node was seen in the majority of those in group 1, there were abnormalities in seven cases, with reduced filling of the sinus node artery in five. In group 2 the sinus node artery filled normally in all cases despite major disease of the parent vessel in three. The combination of contralateral coronary artery disease with extensive atrial anastomoses was actively sought because this arrangement might predispose to a steal phenomenon. Such conditions were fully met in three cases in group 1 and two cases in group 2, and were found to a lesser extent in a further two cases in group 1 and three in group 2.

Although coronary artery disease was unlikely to be the principal cause of sinus node dysfunction in most of the cases studied it was relatively common and may have been a factor in about one third. Improved survival after myocardial infarction may increase the number of patients with chronic sinoatrial disorder of ischaemic origin.

Chronic sinoatrial disorder (sick sinus syndrome) is now one of the commonest conditions treated by pacemaker implantation, yet its aetiology remains in doubt. Acute dysfunction of the sinus node is commonly seen in the early stages of myocardial infarction but it usually disappears within the first 24–48 hours[1] and initially coronary artery disease was assumed to be responsible for most cases of chronic dysfunction.[2–4] More recently this has been disputed and the long term follow up of patients showing sinus node dysfunction in the acute phase of myocardial infarction has produced conflicting results.[5 6] Currently necropsy studies have shown few major lesions of the blood vessels supplying the sinus node,[7–9] but the numbers of cases studied are small and even fewer have been investigated by postmortem angiography. Reviewing the subject Becker concluded that the aetiology remained in doubt and that a full angiographic study of the blood supply to the sinoatrial node was required to assess the role of coronary artery disease.[10] As an additional factor he suggested that there might be a steal phenomenon through atrial collateral vessels, a possibility which had not been previously assessed. Another factor is the improved survival of patients with extensive cardiac infarction in which there may be major obstruction to the sinoatrial artery or its parent vessel.

We have investigated the blood supply to the sinus node by postmortem angiography in patients with chronic sinoatrial disorder. Patients dying of chronic heart block were used as controls because both they and the patients with sick sinus syndrome had been followed up in an identical manner in our department.

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Table 1 *Basic data in the two groups (further details for group 1 are given in the appendix)*

Group	*No*	*Age (yr)* *Mean*	*Age (yr)* *Range*	*Follow up in months* *Mean*	*Follow up in months* *Range*	*Sex (M/F)*	*Paced*
1	25	75	56–92	55	1–186	20/5	19
2	54	78	49–96	37	1–140	39/15	36

Patients and methods

PATIENTS

Most of the material was obtained from patients who died while in the Devon Heart Block and Bradycardia Survey.[11] All subjects were known to have suffered from either sinoatrial disorder or heart block for 28 days or more. For the purposes of analysis they were divided into the following groups:

Group 1 consisted of 25 subjects with chronic sinoatrial disorder. All were known to have had features of sinus node dysfunction for more than a month before death and 23 had been followed up in the Devon Survey. The angiographic findings in four cases were briefly described in 1977.[8]

Group 2 consisted of 54 subjects with normal sinus node function but chronic second or third degree atrioventricular block and who had been followed up in the Devon Survey for one month or more.

Table 1 gives the age at the time of death, the follow up time, and the number of subjects paced in the two groups. The appendix gives further details of the patients in group 1 and table 2 gives electrocardiographic data. Sinus bradycardia was seen in 21 patients and bradycardia with junctional rhythm was present in another three patients. One case (No 207) did not have clinically significant bradycardia but did have episodes of sinoatrial block with sinus pauses lasting up to eight seconds. A further 18 patients had sinus pauses of ≥1·8 s on the standard

Table 2 *Electrocardiographic findings in patients with sinoatrial disorder (group 1)*

Case No	*Sinus bradycardia*	*Sinus* pause*	*Junctional rhythm*	*Tachycardia*	*ECG lowest rate*	*AV conduction*	*ST/T wave abnormalities on entry*
243	+	+	+	Atrial fibrillation	34	RBBB, 1° block, intermittent CHB	
214	+	+			45	CHB	
215	+	+	+		31	Normal	ST depression I aVL, V5–6, T inversion I, aVL
87	+				50	RBBB, intermittent CHB	
50	+	+	+		33	Intermittent 1° block	T inversion I, III, aVL, V3–6
36	+			Atrial tachycardia and fibrillation	24	LAHB, 1° block	
86	+	+		Atrial tachycardia	30	1° block	
69	+		+		37	Normal	ST depression V4–6
18	+	+			38	Normal	
82	+	+		Atrial flutter	25	Normal	
26	+	+		Atrial flutter	50	Normal	
4	+	+	+	Atrial fibrillation	28	Normal	
35	+			Atrial tachycardia	39	Normal	ST depression I, V4–6 T inversion I, II, aVL, V3–6
01	+			Atrial flutter	49	Normal	
10	+	+		Atrial fibrillation	44	Normal	ST depression V4–6, T inversion II, III, aVF,
74–6							
16	+	+	+	Atrial flutter	36	Normal	
39	+	+			39	RBBB, 1° block	
09	+	+			46	Normal	
88	+	+	+	Atrial tachycardia, ventricular tachycardia	42	Normal	
85	+	+	+		34	LAHB	
07		+	+		63	Normal	ST depression V4–6
44			+		41	Normal	
84		+	+	Atrial tachycardia	34	Normal	
35		+	+	Atrial fibrillation	37	Intermittent 1° block	
75	+	+			46	RBBB, intermittent 1° block	

≥1 8 s on standard electrocardiogram (ECG) or ≥2 s or more on ambulant BCG
BBB, right bundle branch block; CHB, complete heart block; LAHB, left anterior hemiblock

electrocardiogram, or $\geqslant 2$ s or more on ambulant electrocardiography. In three patients the relation of the duration of the pauses to the preceding PP intervals was compatible with sinoatrial block. Periods of junctional rhythm occurred in 12 patients and paroxysmal tachycardia was seen in 14. There were major conduction disturbances in three patients and lesser abnormalities such as bundle branch block or first degree block in seven. No conduction abnormalities were seen in 15. By definition second or third degree block was present in all the subjects in group 2 and none had evidence of sinus node dysfunction.

During the period of the study postmortem angiography was carried out on four additional patients who had been seen during the acute stages of myocardial infarction with evidence of sinus node dysfunction. All had periods of sinus arrest and gross bradycardia which persisted up to the time of their death at 4, 15, 16, and 17 days after the acute event.

METHODS

Most of the patients died at home and permission for necropsy was only obtained by the speedy cooperation of the patient's family doctor. Usually the family agreed to only a limited procedure; this was carried out as soon as possible after death. When the heart was removed particular care was taken to sever the superior vena cava 2 or 3 cm above its junction with the right atrium so that the sinoatrial node and its blood supply were not damaged. After initial inspection of the heart the coronary ostia were examined and then cannulated. Both coronary arteries were flushed with saline at low pressure to remove postmortem sludge and then the right coronary was perfused with a radio-opaque medium for 5 min at a pressure of 130 mm Hg. Radiographs of the heart were taken in three planes on a fine grain film (Mamoray RP3) with an Elema-Schonander skull unit with 40 kV at 400 mA, a focal spot of 0·6 mm, and a focal film distance of 32 inches. Films were developed and if they were satisfactory, then the left coronary artery was perfused and a further set of *x* rays was taken. The standard views were anterior-posterior, left lateral, and left anterior oblique; but in a proportion of patients additional views were taken. The injectate usually consisted of a barium suspension mixed with Colourpaque to which a little dissolved gelatine had been added. This mixture penetrated into vessels with diameters of between 25 and 30 μm.

After postmortem angiography of the heart in toto, we removed the block of tissue containing the junction between the superior vena cava and right atrium, pinned it out on a board, and *x* rayed it to demonstrate the sinoatrial node artery and its branches. The heart was fixed for two or three weeks and blocks taken from the heart and main coronary arteries for histological examination.[8] We used a modification of the method described by Davies.[12] The angiograms were studied with an overhead projector which gave a ninefold magnification. We concentrated on the right coronary up to the origin of the posterior descending branch (where present) and the left coronary, including the initial parts of its two main branches proximal to the first diagonal and second obtuse marginal. The widths of the arteries were measured and in narrowed areas the reduction in lumen was expressed as a percentage of the width of the preceding sections; obstructions of less than 20% were classified as normal. We looked for vessels running between branches of the sinoatrial node artery or its parent vessel and other atrial arteries, particularly those arising from the contralateral coronary artery. To be accepted as anastomotic vessels they had to be seen on all three *x* ray projections (fig 1). One or two connecting vessels were designated as "some" and three or more as "many". If filling of atrial arteries stemming from the right coronary artery was poor after this vessel had been perfused, the appearances were reviewed after perfusion of the left coronary artery for evidence of an increased flow of contrast material via anastomoses. The potential for a steal phenomenon was identified only if there was an anastomosis between the sinus node artery proximal to the node and a branch of an obstructed (50% or more) contralateral artery.

Filling of the sinoatrial node artery was assessed by examination of the initial angiograms of the whole heart and subsequent films of the tissue block containing the sinoatrial node. Filling was classified as "normal" where the vessel and its tributaries could be seen easily with sharp outlines on a standard *x* ray viewing box and "reduced" if the vessel was blurred with indistinct or barely visible tributaries. Filling was termed "poor" if the sinus node artery could only be discerned with difficulty using a bright light and "nil" if the artery was invisible on *x* rays of the whole heart or tissue block containing the sinus node.

The right coronary artery was identified as being dominant if it gave rise to the posterior descending artery.[13]

Results

The left coronary artery was dominant in 10 of the 25 cases in group 1 and 15 of the 54 cases in group 2. The origin of the sinus node artery was easily identified in all patients except case 187 in group 1, in whom the left coronary artery was normal but did

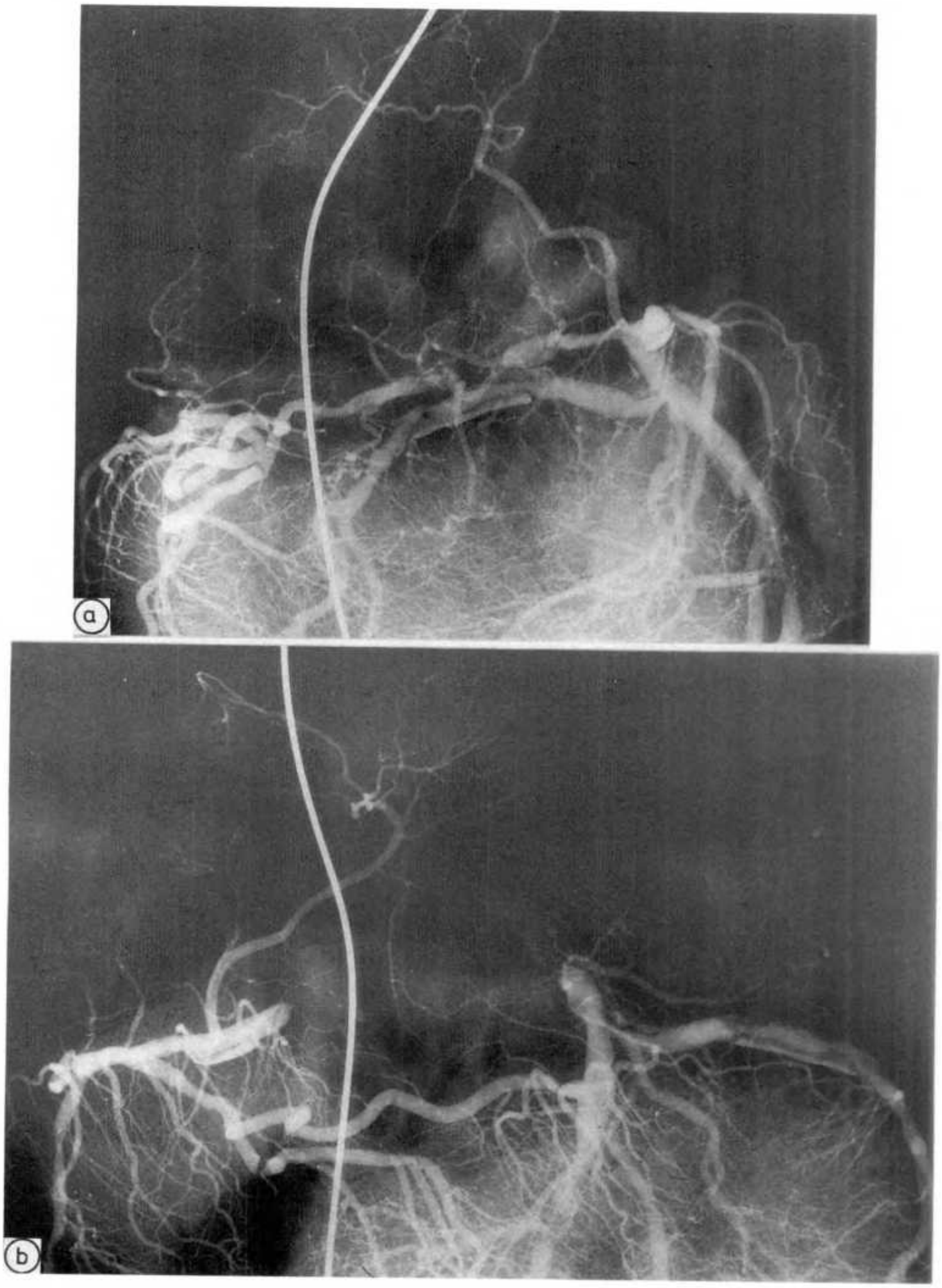

Fig 1 *Angiograms of case 118 with both coronary arteries perfused and showing a large atrial artery arising from the right coronary artery which supplies the sinus node area. The oblique view (a) appears to show a series of anastomoses but the arterior-posterior view (b) shows separation of the vessels particularly in the upper atrium.*

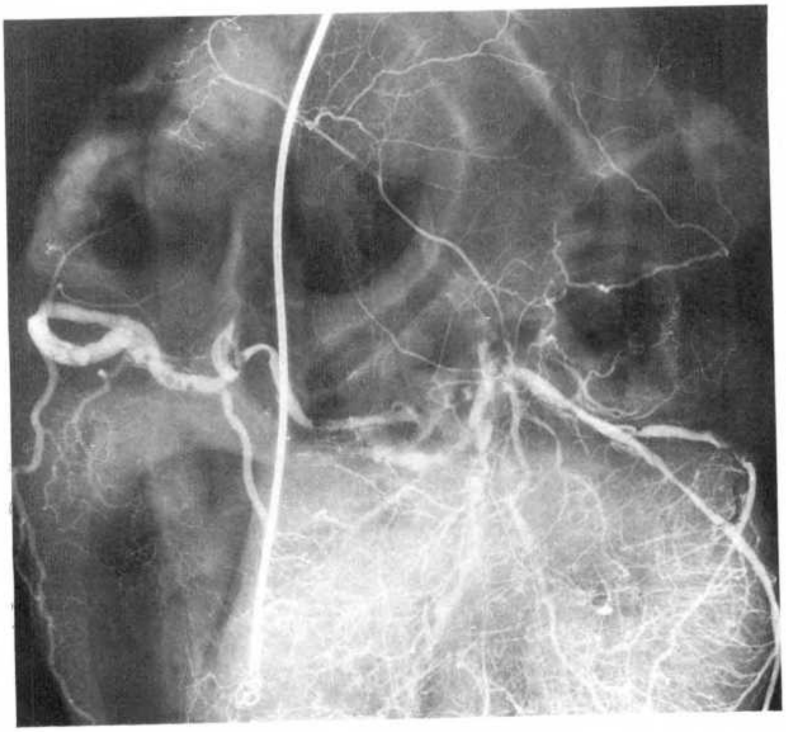

Fig 2 *Anterior-posterior angiogram of case 243 after perfusion of both coronary arteries, showing gross general arterial disease but normal filling of the sinoatrial node artery which arises close to the origin of the left circumflex coronary artery.*

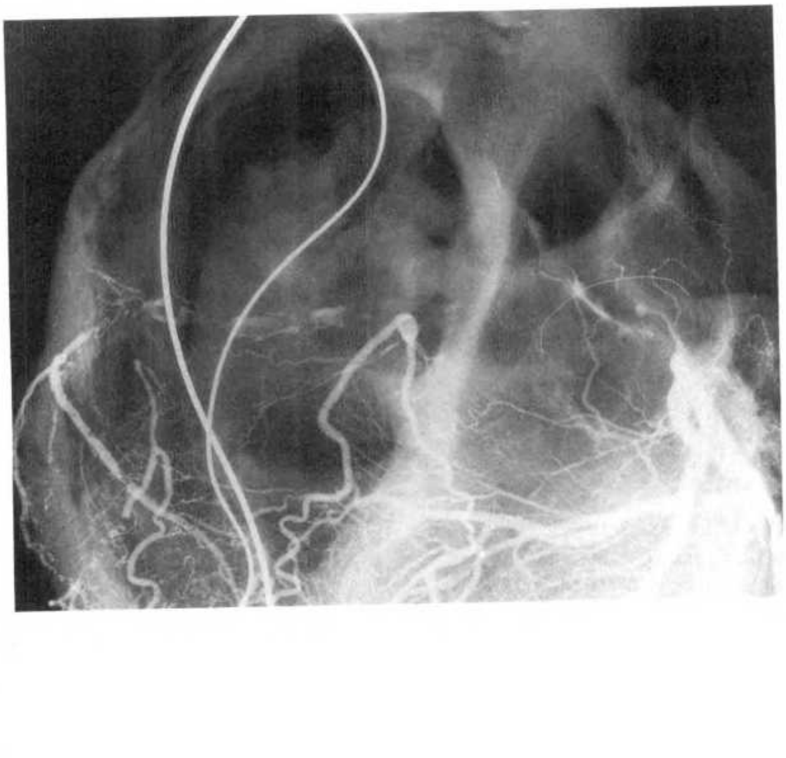

Fig 3 *Anterior-posterior angiogram of case 187 after perfusion of both coronary arteries. The right main coronary immediately distal to the conus artery was completely blocked. There was no filling of the atrial arterial branches on the right side.*

Table 3 *Arteriographic findings in all the patients in group 1 and in the 18 cases from group 2 showing arterial obstructions of ≥20% in one or more of the major vessels*

			Coronary supplying sinoatrial node				
Case No	*Dominant coronary artery*	*SANA filling*	*Side*	*Proximal**	*Distal**	*Contralateral coronary artery*	*Atrial anastomoses*
Group 1							
243	L	Normal	L	50%	50%	90%	Some
214	L	Normal	L	Normal	Normal	Normal	Some
215	R	Normal	R	Normal	Normal	LAD blocked	Many
187	L	Nil	R	Blocked	Blocked	Normal	None
150	R	Normal	R	Normal	Normal	LAD blocked, circ 30%	Some
36	R	Normal	R	Normal	Normal	Normal	None
186	R	Normal	L	Normal	Blocked	20% proximal	Many
169	L	Normal‡	R	>90%	20%	40% main	Many†
118	R	Normal	R	Normal	Normal	Normal	None
82	R	Normal	R	Normal	Normal	Normal	Some
226	R	Normal	L	Normal	Normal	Normal	Some
4	R	Normal	R	Normal	Normal	Normal	None
35	L	Reduced	L	75%	Circ 60%, LAD blocked	40%	None
101	R	Normal	R	Normal	35%	Normal	Some
210	L	Normal	R	Normal	50%	80% main, 40% circ, 80% LAD	Some
216	R	Poor	R	>90%	60%	Circ blocked	None
39	L	Normal	L	Normal	Normal	Normal	Some
209	R	Normal	R	Normal	Normal	Normal	Some
88	R	Normal	R	Normal	35%	50% main, circ blocked	Many
185	L	Nil	L	35%	Normal	Normal	None
207	R	Poor	L	90%	80%	Normal	Some†
144	L	Normal	R	Normal	35%	50% circ	None
184	L	Normal	R	Normal	Normal	Normal	Some
135	R	Normal	R	Normal	Normal	Normal	Some
75	R	Normal	R	Normal	Normal	Normal	Many
Group 2							
146	L	Normal‡	R	90%	Blocked	50% LAD	Many†
86	R	Normal	L	80%	70%	50%	Some
148	R	Normal	R	Normal	40%	60% LAD, 40% circ	Some
61	R	Normal	R	Normal	Normal	LAD blocked, 80% circ	Some
7	R	Normal	R	Normal	Normal	40% circ	Some
94	L	Normal	R	Normal	50%	50% LAD	Some
26	R	Normal	R	Normal	65%	50% LAD	None
162	L	Normal‡	R	Blocked	Normal	30% LAD	Many†
48	L	Normal	R	Normal	20%	40% LAD	Some
50	R	Normal	R	Normal	Normal	20% LAD	Some
151	L	Normal	R	50%	Normal	30% LAD	Some
80	R	Normal	L	Normal	Normal	50%	None
108	R	Normal	R	Normal	50%	Normal	None
95	L	Normal	R	Normal	Normal	50% LAD	Some
125	R	Normal	R	25%	Normal	50% main, 25% circ	Some
81	R	Normal	L	Normal	20%	Normal	None
205	L	Normal	L	40%	Normal	Normal	None
136	R	Normal	L	30%	90% LAD	20%	Some

*To sinoatrial node artery; †apparent filling towards SANA; ‡normal filling after perfusion of left coronary artery.
LAD, left anterior descending artery; circ, circumflex artery; SANA, sinoatrial node artery.

not give rise to any large atrial branches while the right coronary was completely blocked close to its origin. In this case the right coronary was believed to be the parent vessel supplying the sinoatrial node artery. So the blood supply to the sinus node came from the right coronary artery in 17 (distal in one) and the left coronary artery in eight cases (distal in three) in group 1 and from the right coronary artery in 35 (distal in three) and the left coronary artery in 19 cases (distal in one) in group 2.

SINUS NODE ARTERY AND ITS PARENT VESSEL

In most subjects from both groups the sinus node artery filled normally, often despite evidence of extensive coronary artery disease (fig 2). In group 1, however, narrowing of ≥50% was present in seven cases and sinus node artery filling was abnormal in six (table 3). Figure 3 shows examples in which there was no filling of the sinus node area and fig 4 shows the sinus node artery filled through anastomotic connections from the contralateral coronary vessel.

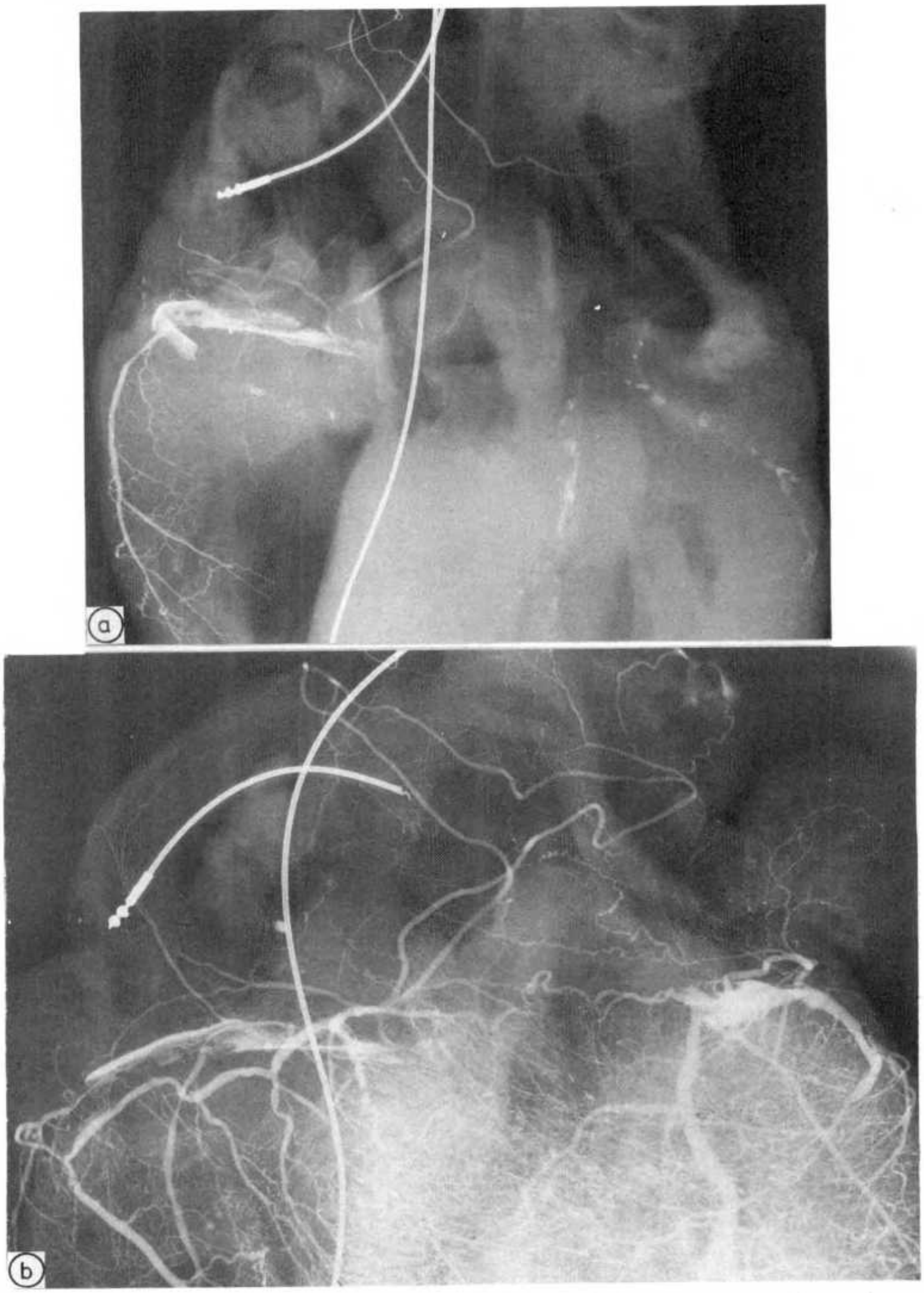

Fig 4 *Anterior-posterior angiograms of case 169: (a) perfusion of the right coronary shows that this was almost completely obstructed close to its origin. The sinus node artery filled but to a reduced extent and smaller tributaries cannot be seen; (b) taken after both coronaries had been perfused, showing increased filling of the sinus node artery and adjacent vessels.*

Table 4 *Origin of the sinoatrial node artery in groups 1 and 2 compared with that described by James*[18] *and Hutchinson*[19]

	Group 1		*Group 2*		*James*		*Hutchinson*	
Artery	*No*	%	*No*	%	*No*	%	*No*	%
Right proximal	16	64	32	59	55	52	19	48
Right distal*	1	4	3	6	2	2	7	18
Left proximal	5	20	18	33	43	41	11	28
Left distal*	3	12	1	2	2	2	3	8
Total	25		54		106†		40	

*The second (intermediate) and third (posterior) parts of the artery.
†Including two with dual supply and two with unknown origin.

Case 185 was unusual because the atrial artery supplying the branch to the sinus node was blocked at a point approximately two thirds along its course.

The sinus node artery filled normally in all of the 54 subjects in group 2. There was a major obstruction of the parent vessel in three, however, and in cases 162 and 146 the right main coronary artery was completely blocked and the sinus node artery filled via extensive anastomotic networks coming from the left coronary. In case 86 the sinus node artery was a branch of the left coronary, which was 80% narrowed; initial injection of the right coronary artery produced some filling by anastomotic channels and filling through the left coronary was normal.

CONTRALATERAL CORONARY ARTERY

In seven cases in group 1 the contralateral artery or one of its major branches was obstructed by ≥50%. Two of these (216 and 144) had no apparent anastomotic vessels, but in the other five the findings were compatible with a steal phenomenon because there were some or many anastomotic vessels associated with major obstruction of the contralateral coronary artery.

In group 2 there was ≥50% obstruction of the contralateral artery or its main branches in nine, including two of those with major disease of the other coronary artery. None of the remaining seven cases had many anastomotic vessels: five had some and two had none.

In the four patients dying soon after acute myocardial infarction postmortem angiography showed that the parent vessel to the sinus node artery was completely blocked in two and that there was severe bilateral coronary disease in the other two cases, one of which also fulfilled the criteria for a potential steal phenomenon.

Discussion

The anatomy of the blood supply to the atria and sinus node is very variable[14–16] and if sinus node dysfunction were usually the result of ischaemia it might be expected that certain anatomical patterns would be unduly common in this condition because they predisposed the area to ischaemia.[17] Conversely other vascular configurations might reduce the risk of hypoxia because they give considerable scope for anastomosis between the different arterial branches to the atrium.[18, 19] Nerantzis and Avgoustakis suggest that the so-called S shaped sinus node artery arising from the distal part of the left circumflex may be particularly beneficial in cases of atherosclerosis, since it can function as a bridge between the two major coronary trunks.[20] This makes the sinus node area in a heart "much less vulnerable to atherosclerotic disease than would be the case otherwise". In practice, the basic coronary anatomy of the subjects of the present study was generally similar in groups 1 and 2 and findings in both groups resembled those in other series of subjects without sinus node disease (table 4).

It is unwise to make dogmatic deductions from necropsy angiograms about the likely state of the circulation in life, because the static filling pressure applied to dead vessels must be very different from the pulsatile flow occurring in the live circulation. The steady pressure of 130 mm Hg that was used would tend to fill peripheral vessels even if a major obstruction was present, yet under such circumstances in life tissue ischaemia might be expected, particularly when under increased load. Also the degree of coronary spasm cannot be assessed and there is evidence that spasm is often present in atheromatous heart disease. The influence of extracardiac anastomotic vessels[21] could not be assessed in this study and even intercoronary anastomoses may have been difficult to identify. Radiographs taken in a single plane may be misleading since vessels appear to criss-cross each other and the scope for anastomosis may seem very great. Further views, however, will disclose the true arrangement and with three projections it is usually possible to confirm the presence of collateral channels. In some instances we studied up to six views after each injection but the additional plates did not materially add to the information. When collaterals are found it may be difficult to assess their importance because they vary considerably in size, length, and morphology.

In most patients with chronic sinoatrial disorder in the present study the blood supply to the sinus node was not obstructed by disease of the large arteries. Significant arterial lesions were relatively common, however; and these caused reduced filling of the sinoatrial node artery in five of 25 cases and the potential for a steal phenomenon in a further five cases. There is some uncertainty about the effects of the lesions in two of these cases (215 and 150) where the principal contralateral arterial lesions were in the anterior descending branch of the left coronary artery, a vessel which contributes less to the atrial anastomotic system than do the circumflex and right coronary arteries. All of the cases in group 2 showed satisfactory filling of the sinus node artery, although in three collateral vessels from the contralateral coronary artery made a major contribution. The angiographic appearance suggested a potential for a steal phenomenon in five cases, but in three the predominant obstruction was in the left anterior descending artery. There had been no evidence of sinus node dysfunction during life in any of these cases. The findings in the four cases of acute sinus node dysfunction after cardiac infarction suggest that, had they survived, at least three would have been left with ischaemia of the sinus node. Improved methods of treatment may increase the number of patients with impaired sinoatrial function who survive the acute episode.

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References

1 Fluck DC, Olsen E, Pentecost BL, *et al.* Natural history and clinical significance of arrhythmias after acute cardiac infarction. *Br Heart J* 1967;**29**:170–89.
2 Conde CA, Leppo J, Lipski J, *et al.* Effectiveness of pacemaker treatment in the bradycardia-tachycardia syndrome. *Am J Cardiol* 1973;**32**:209–14.
3 Hartel G, Tarvensaari T. Treatment of sinoatrial syndrome with permanent cardiac pacing in 90 patients. *Acta Med Scand* 1975;**198**:341–7.
4 Scarpa WJ. The sick sinus syndrome. *Am Heart J* 1976;**92**:648–60.
5 Parameswaran R, Ohe T, Goldberg H. Sinus node dysfunction in acute myocardial infarction. *Br Heart J* 1976;**38**:93–6.
6 Hatle T, Bathen J, Rokseth R. Sinoatrial disease in acute myocardial infarction. Long-term prognosis. *Br Heart J* 1976;**38**:410–4.
7 Davies MJ, Anderson RH, Becker AE. *The conduction system of the heart*. London: Butterworth, 1983.
8 Evans R, Shaw DB. Pathological studies in sinoatrial disorder (sick sinus syndrome). *Br Heart J* 1977;**39**:778–86.
9 Thery C, Gosselin B, Lekieffre J, Warembourg H. Pathology of sinoatrial node. Correlation with electrocardiographic findings in 111 patients. *Am Heart J* 1977;**93**:735–40.
10 Becker AE. General comments. In: Bonke FIM, ed. *The sinus node, structure, function and clinical relevance*. The Hague: Martins Nijhoff Medical Division, 1978.
11 Shaw DB, Kekwick CA. Potential candidates for pacemakers. *Br Heart J* 1978;**40**:99–105.
12 Davies MJ. A histological study of the conduction system in complete heart block. *J Pathol Bacteriol* 1967;**94**:351–8.
13 Boucek RJ, Morales AR, Romanelli R, Judkins MP. *Coronary artery disease. Pathologic and clinical assessment*. Baltimore: Williams and Wilkins, 1984.
14 Spalteholz W. *Die Arterien der Herzwand, Anatomische Untersuchungen en Menschen-und Tierherzen*. Leipzig: S Hirzel, 1924.
15 Campbell JS. Stereoscopic radiography of the coronary system. *Q J Med* 1929;**22**:247–67.
16 James TN, Burch GE. The atrial coronary arteries in man. *Circulation* 1958;**17**:90–8.
17 Gazetopoulos N, Ioannidis PJ, Marselos A, *et al.* Length of main left coronary artery in relation to atherosclerosis of its branches: a coronary arteriographic study. *Br Heart J* 1976;**38**:180–5.
18 James TN. *Anatomy of the coronary arteries*. New York: Paul B Hoeber, 1961.
19 Hutchinson MCE. A study of the atrial arteries in man. *J Anat* 1978;**125**:39–54.
20 Nerantzis C, Avgoustakis D. A S-shaped atrial artery supplying the sinus node artery. An anatomical study. *Chest* 1973;**2**:274–8.
21 Petelenz T. Extra-coronary blood supply of the sinoatrial node. *Cardiologia* 1965;**47**:57–67.

Appendix *Basic data in group 1*

Case No	*Age at death*	*Sex*	*Follow up (mth)*	*Symptoms and signs*	*Paced/unpaced*	*Cause of death*
243	92	M	186	Syncope, dyspnoea	Paced	Cerebrovascular accident
214	80	F	155	Syncope, dyspnoea	Paced	Cerebrovascular accident
215	69	F	144	Syncope, dyspnoea	Paced	Myocardial infarction
187	79	M	121	Dizziness, dyspnoea, chest pain	Paced	Carcinoma/bronchus
150	85	M	97	Syncope, dyspnoea	Paced	Cerebrovascular accident
36	64	F	89	Syncope, dyspnoea, chest pain	Paced	Left ventricular failure
186	82	M	79	Syncope, dyspnoea	Paced	Bronchopneumonia
169	63	M	78	Cardiac failure, chest pain	Paced	Myocardial infarction
118	56	M	71	Dizziness, dyspnoea	Paced	Unknown
82	60	F	57	Syncope, dyspnoea	Paced	Cerebrovascular accident
226	77	M	49	Syncope	Paced	Carcinomatosis
4	65	F	58	Syncope, dyspnoea, cardiac failure	Paced	Pacemaker failure
35	69	M	58	Dyspnoea, chest pain	Unpaced	Myocardial infarction
101	87	M	30	Syncope	Unpaced	Bronchopneumonia
210	70	M	29	Syncope, dyspnoea	Paced	Cardiac failure
216	70	M	14	Dizziness	Paced	Carcinoma/oesophagus
39	88	M	12	Dizziness	Unpaced	Bronchopneumonia
209	77	M	9	Syncope	Paced	Cerebrovascular accident
88	76	M	8	Syncope, cardiac failure	Unpaced	Cardiac failure
185	85	M	7	Syncope	Unpaced	Unknown
207	78	M	5	Syncope, cardiac failure	Paced	Renal failure
144	82	M	4	Dizziness, dyspnoea, chest pain	Unpaced	Unknown but sudden
184	65	M	2	Syncope, dyspnoea	Paced	Cardiac failure
135	76	M	1	Syncope, cardiac failure	Paced	Unknown
75	83	M	1	Syncope	Paced	Cardiac failure

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Percutaneous balloon dilatation of aortic valve stenosis in neonates and infants

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SUMMARY Percutaneous balloon dilatation of severe aortic valve stenosis was attempted in thirteen patients (seven neonates and six infants). In two the valve could not be crossed and both died during subsequent operation. Two patients died during manipulation of the balloon catheter. No significant benefit was obtained in another patient who later died during operation. Balloon dilatation was successful in the remaining eight patients, reducing the aortic valve pressure gradient from a mean of 63 mm Hg (95% confidence interval 38 to 88 mm Hg) to a mean of 23 mm Hg (95% confidence interval 7 to 39 mm Hg). Two of these patients subsequently died from heart failure related to other cardiac lesions. The six survivors have done well. At follow up the maximum Doppler velocities in the ascending aorta ranged from 1·9 to 4·0 m/s after 2–23 months, but despite this evidence of an increasing valve gradient there has been lasting clinical improvement.

The development of balloon dilatation has altered the management of many stenotic lesions in paediatric cardiology and the technique is already widely used for relief of pulmonary valve stenosis and recoarctation of the aorta. In most other situations balloon dilatation remains experimental and will only supersede operative management if it can equal or improve upon the results of surgery.

The treatment of critical aortic valve stenosis in infancy is difficult and the surgical mortality is high.[1 2] Palliation by surgical valvotomy may produce long lasting benefit but repeat operation is often necessary and is associated with a higher mortality.[3] If the efficacy, morbidity, and mortality of balloon dilatation can match the results of surgical valvotomy in these patients, it may provide an attractive alternative approach to initial management. Isolated reports of successful balloon dilatation in infancy, however, may give a falsely optimistic impression of the procedure.[4–6] This paper reports our experience in 13 consecutive patients who were younger than 12 months and had aortic valve stenosis.

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Patients

Between June 1985 and April 1987 seven nenonates and six infants underwent cardiac catheterisation with a view to performing balloon dilatation of severe aortic valve stenosis (table). Their ages ranged from one day to 11 months (median four weeks) and their weights from 1·5 to 8·9 kg. Ten patients had signs of heart failure and three had already undergone surgical valvotomy. One patient (case 3) had coexisting severe mitral valve stenosis. Patient 10 was born 14 weeks prematurely and developed bronchopulmonary dysplasia despite ligation of the ductus arteriosus. Patient 6 was born at 26 weeks' gestation and in addition to critical aortic stenosis she had severe left ventricular dysfunction and mitral valve stenosis, and subsequently underwent ligation of a ductus arteriosus.

The electrocardiogram demonstrated left ventricular hypertrophy in all patients, with repolarisation abnormalities in six. Echocardiography showed hypertrophy, dilatation, and impaired contraction of the left ventricle in five patients and small ventricles with concentric hypertrophy in the remainder; two of these having very small left ventricular cavities similar to those seen in the hypoplastic left heart syndrome (table).

Table *Details of patients with aortic stenosis treated by balloon dilatation*

Patient	*Age*	*Weight (kg)*	*LV function*	*Balloon diameter (mm)*	*AOV gradient (mm Hg)*		*AR grade*	*Follow up (months)*	*Doppler (m/s)*	*Comments*
					Before	*After*				
1	1 day	2·2	H	—	—	—	—	—	—	Valve not crossed, died after operation
2	6 day	3·0	S	—	93	—	—	—	—	Died during balloon catheter manipulation
3	13 day	2·8*	D	6	64	44	0	—	—	Died in heart failure from mitral stenosis
4	14 day	3·5	H	6	7	19	0	23	1·9	Ventricular function has improved
5	21 day	3·8	D	7	86	5	0	13	3·1	Remains well
6	22 day	1·5	D	5	40	10	1–2	—	—	Died from persisting heart failure
7	28 day	3·0*	S	6	50	—	—	—	—	Died after aortic root replacement
8	30 day	3·5	S	6	50	30	0	2	4·0	Remains well
9	2 mth	4·2	D	6	60	—	—	—	—	Died during balloon inflation
10	5 mth	5·6	S	8	103	6	1	8	2·8	Remains well
11	7 mth	6·9	D	8	80	60	0	14	3·5	Remains well
12	8 mth	4·2	S	—	—	—	—	—	—	Valve not crossed, died after operation
13	11 mth	8·9*	S	9	76	9	1	13	2·5	Remains well

AOV, aortic valve; AR, aortic regurgitation; D, dilated hypertrophic left ventricle; H, hypoplastic left ventricle; LV, left ventricle; S, small hypertrophied left ventricle; *previous surgical valvotomy.

Methods

Cardiac catheterisation was performed under general anaesthetic in ten patients and with sedation and local anaesthesia in three. Catheters were introduced by percutaneous femoral artery puncture in five patients and by elective femoral artery cut down in the remainder. Heparin (100 units/kg body weight) was given. The balloon chosen was at least 1–2 mm smaller than the valve diameter measured from a cineaortogram. The aortic valve was crossed with an end-hole catheter, usually with the help of a guide wire. The balloon catheter was advanced over an exchange guide wire with no arterial sheath. The balloon was positioned across the valve and inflated 1–4 times to produce and then to abolish waisting (fig 1). The catheter was then withdrawn and the pressure measurements (fig 2) and aortogram were repeated. In these small ill patients the procedure was kept as short as possible. Right heart catheterisation was not performed and no measurement of cardiac output or estimation of aortic valve area was possible.

Results

Balloon dilatation was accomplished safely in nine patients (table). In two further patients the aortic valve could not be crossed; both were referrred for open valvotomy and both died after operation. One patient died during manipulation of the balloon catheter around the aortic arch when only the guide wire was across the aortic valve. Permission for a necropsy was refused and the cause of death was not established. Another patient became asystolic after the first balloon inflation and could not be resuscitated. At necropsy there was no evidence of aortic rupture or other structural damage. The valve was dysplastic with three thickened leaflets and distinct commissures. Comparison with the echocardiogram and aortogram obtained before balloon dilatation suggested that the valve had split along the commissures. In one patient whose femoral artery was damaged during exchange of balloon catheters no post-dilatation pressures could be recorded. There was no clinical improvement and the patient died after attempted replacement of the aortic root.

After balloon dilatation pressures were recorded in eight patients and in seven of these the valve gradients before dilatation were between 40 and 103 mm Hg (mean 63 mm Hg, 95% confidence interval 38 to 88 mm Hg) (fig 3). In patient 4 the aortic valve gradient measured only 7 mm Hg but there was clinical evidence of a very low cardiac output and the clinical, echocardiographic, and angiographic diagnosis was severe aortic valve stenosis with a small, poorly functioning left ventricle.

The diameters of the inflated balloon catheters used were between 5 and 9 mm. In seven of the nine patients smaller balloon catheters were used initially but did not produce satisfactory results. Attempts to insert an 8 mm balloon in patient 7 caused laceration of the femoral artery and the procedure was abandoned. In patient 11 a 10 mm balloon catheter could

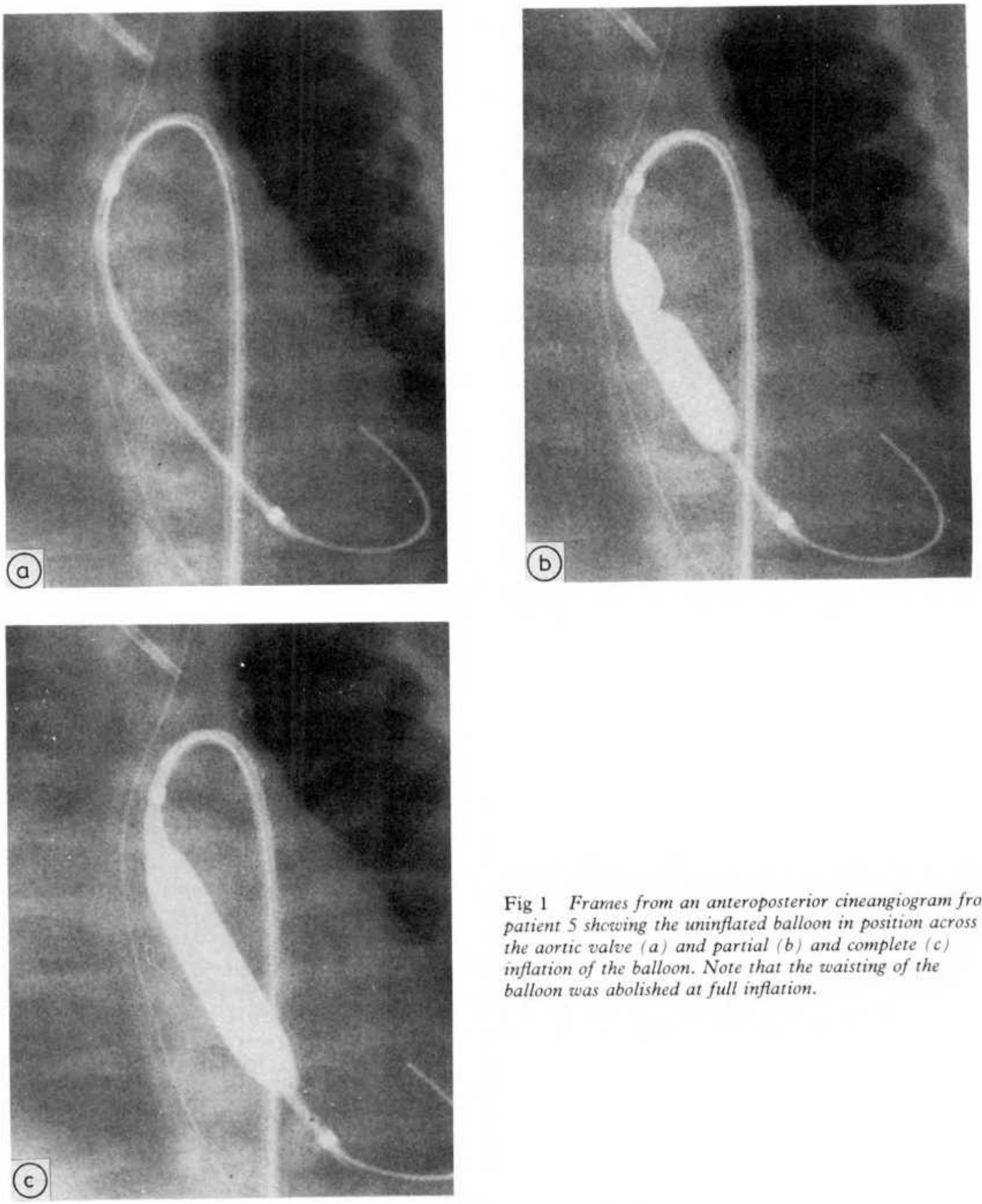

Fig 1 *Frames from an anteroposterior cineangiogram from patient 5 showing the uninflated balloon in position across the aortic valve (a) and partial (b) and complete (c) inflation of the balloon. Note that the waisting of the balloon was abolished at full inflation.*

not be introduced into the femoral artery. In both these patients the result achieved with smaller balloons was disappointing.

After balloon dilatation the peak to peak systolic pressure gradient was reduced in the seven patients who had considerable gradients initially (fig 3) and had increased in patient 4. The residual gradients were between 5 and 60 mm Hg (mean 23 mm Hg, 95% confidence interval 7 to 39 mm Hg). Repeat aortic angiography did not show appreciable aortic

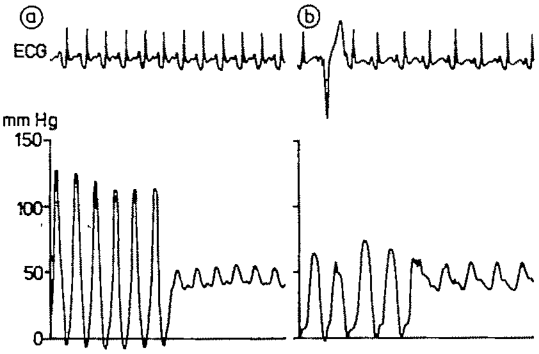

Fig 2 *Pressure recordings during catheter withdrawal from the left ventricle to the ascending aorta in patient 5 (a) before and (b) after balloon dilatation.*

regurgitation (table).

Seven of the 13 patients in this series died—two during the procedure (as described above), three during subsequent operation, and two in the month after balloon dilatation. Both of the last patients still required artificial ventilation for intractable pulmonary oedema. Patient 3 had severe mitral valve stenosis and patient 6 had mitral valve stenosis and severely impaired left ventricular function that failed to improve despite effective balloon dilatation and ligation of a ductus arteriosus.

Two of the six survivors had occlusion of the femoral artery after balloon dilatation (one had had percutaneous puncture and the other a cut down on the femoral artery) and both underwent successful femoral artery embolectomy. There were no arterial complications in the other four patients, two of whom had percutaneous puncture while the other two underwent femoral artery cut down.

At follow up examination after 2–23 months all six patients were well. None had signs of heart failure or required diuretic treatment. Non-invasive assessment included Doppler echocardiography. Maximum velocities in the ascending aorta at the most recent examination ranged from 1·9 to 4·0 m/s (table) and correlated well with the measured gradient in the two patients who underwent repeat cardiac catheterisation.

Discussion

At first sight the results achieved in this series appear disappointing, with seven deaths and six survivors. None the less, three patients were only included because they had significant residual aortic stenosis causing persisting heart failure after surgical valvotomy and three others because they were unsuitable for operation—one weighed only 1·5 kg (patient 6) and in two others the left ventricle was thought to be too small for long term survival (patients 1 and 4). Three of the seven deaths occurred during subsequent operation and were not related to the balloon procedure. Two further deaths resulted from persisting heart failure related to other cardiac lesions.

None of the five patients weighing ⩽3 kg survived long term. In comparison, only two of eight patients larger than 3 kg died, one of them during a subsequent surgical operation. Thus small size is an important risk factor, probably partly for technical reasons, but mainly because those with the most severe valve stenosis, the most important associated lesions, and the worst clinical condition will tend to present earliest.

Balloon dilatation of the aortic valve in these small patients is technically difficult. Introduction of the balloon catheter into the femoral artery risks damage to the vessel.[7] Our results show that both cut down and percutaneous puncture may be complicated by arterial occlusion and neither approach has been shown to be better. In no case was arterial access not achieved, but in two patients the aortic valve could not be crossed and a surgical valvotomy was then the only option.

Death during balloon dilatation of the aortic valve in infancy has been reported before and was found at necropsy to be caused by laceration of the aortic wall.[8] This was attributed by the authors to the balloon bursting in the ascending aorta but may have resulted from manipulation of the balloon catheter in the aortic arch. The balloon did not burst during

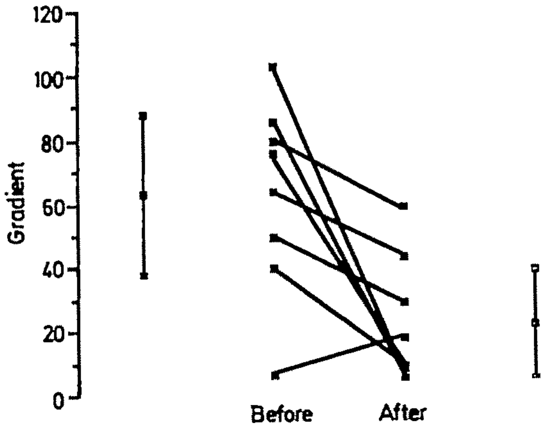

Fig 3 *Peak to peak pressure gradients between left ventricle and ascending aorta before and after balloon valvotomy. Vertical bars indicate 95% interval. The mean gradient was reduced from 63 mm Hg (95% confidence interval 38 to 88 mm Hg) to 23 mm Hg (95% confidence interval 7 to 39 mm Hg).*

treatment of either of our patients who died during the procedure, and the aorta was intact in the case examined at necropsy.

Rupprath and Neuhaus reported success using coronary balloon catheters of up to 4·2 mm.[5 9] In five of our nine patients initial results with balloons measuring 3·5–10 mm in diameter were inadequate and we would not recommend use of coronary balloon catheters except in very small babies. On the other hand, it is important that balloons with diameters larger than the aortic valve ring are not used. Intraoperative dilatation with oversize balloons in neonates produces a high incidence of fatal aortic valve damage.[10]

Follow up assessment by Doppler echocardiography has suggested that the aortic valve gradients are increasing. This may reflect an increase in the severity of the valve stenosis, or the difference between catheter and Doppler measurement of valve stenosis, or (perhaps more likely) an improvement in cardiac output after reduction of the obstruction. All follow up examinations were outpatient procedures performed without sedation and instantaneous peak velocity was measured.

An improvement in the results of percutaneous balloon dilatation of aortic valve stenosis in this difficult group of patients can be expected with increasing practical experience, developments in balloon catheter design, and, perhaps, better patient selection. The procedure may provide an alternative to initial surgical management in some patients. Relief of aortic valve stenosis in patients weighing <3 kg, however, is likely to continue to have a significant mortality, whether performed surgically or by catheter.

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References

1 Sink JD, Smallhorn JF, Macartney FJ, Taylor JFN, Stark J, de Leval MR. Management of critical aortic stenosis in infancy. *J Thorac Cardiovasc Surg* 1984;87:82–6.

2 Duncan K, Sullivan I, Robinson P, Horvath P, de Leval M, Stark J. Transventricular aortic valvotomy for critical aortic stenosis in infants. *J Thorac Cardiovasc Surg* 1987;93:546–50.

3 Binet JP. Critical aortic stenosis: surgical results in infancy. In: Doyle EF, Engle MA, Gersony WM, Rashkind WJ, Talner NS, eds. *Pediatric cardiology*. New York: Springer Verlag, 1986:653–6.

4 Sanchez GR, Mehta AV, Ewing LL, Brickley SE, Anderson T, Black IFS. Successful percutaneous balloon valvuloplasty of the aortic valve in an infant. *Pediatr Cardiol* 1985;6:103–6.

5 Rupprath G, Neuhaus KL. Percutaneous balloon aortic valvuloplasty in infancy and childhood. In: Doyle EF, Engle MA, Gersony WM, Rashkind WJ, Talner NS, eds. *Pediatric cardiology*. New York: Springer Verlag, 1986:331–3.

6 Lababidi Z, Weinhaus L. Successful balloon valvuloplasty for neonatal critical aortic stenosis. *Am Heart J* 1986;112:913–6.

7 Keane JF, Helgason H, Fellows KE, Lock JE. Results and complications of balloon valvotomy for congenital aortic stenosis [Abstract]. *Circulation* 1986;74 (suppl II):II–2.

8 Waller BF, Girod DA, Dillon JC. Transverse aortic wall tears in infants after balloon angioplasty for aortic valve stenosis. *J Am Coll Cardiol* 1984; 4:1235–41.

9 Rupprath G, Neuhaus KL. Percutaneous balloon valvuloplasty for aortic valve stenosis in infancy. *Am J Cardiol* 1985;55:1655–6.

10 Phillips RR, Gerlis LM, Wilson N, Walker DR. Aortic valve damage caused by operative balloon dilatation of critical aortic valve stenosis. *Br Heart J* 1987; 57:168–70.

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References: 1. Bang HO, Dyerberg J. Adv Nutr Res 1980; 3: 1-22. 2. Saynor R, Gillott T, Doyle T, *et al.* Prog Lipid Res 1986; 25: 211-217. 3. Nestel PJ. Am J Clin Nutr 1986; 43: 752-757. 4. Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. The Lancet 15 July 1978; 2: 118-119. 5. Saynor R, Verel D, Gillott T. Atherosclerosis 1984; 50: 3-10.

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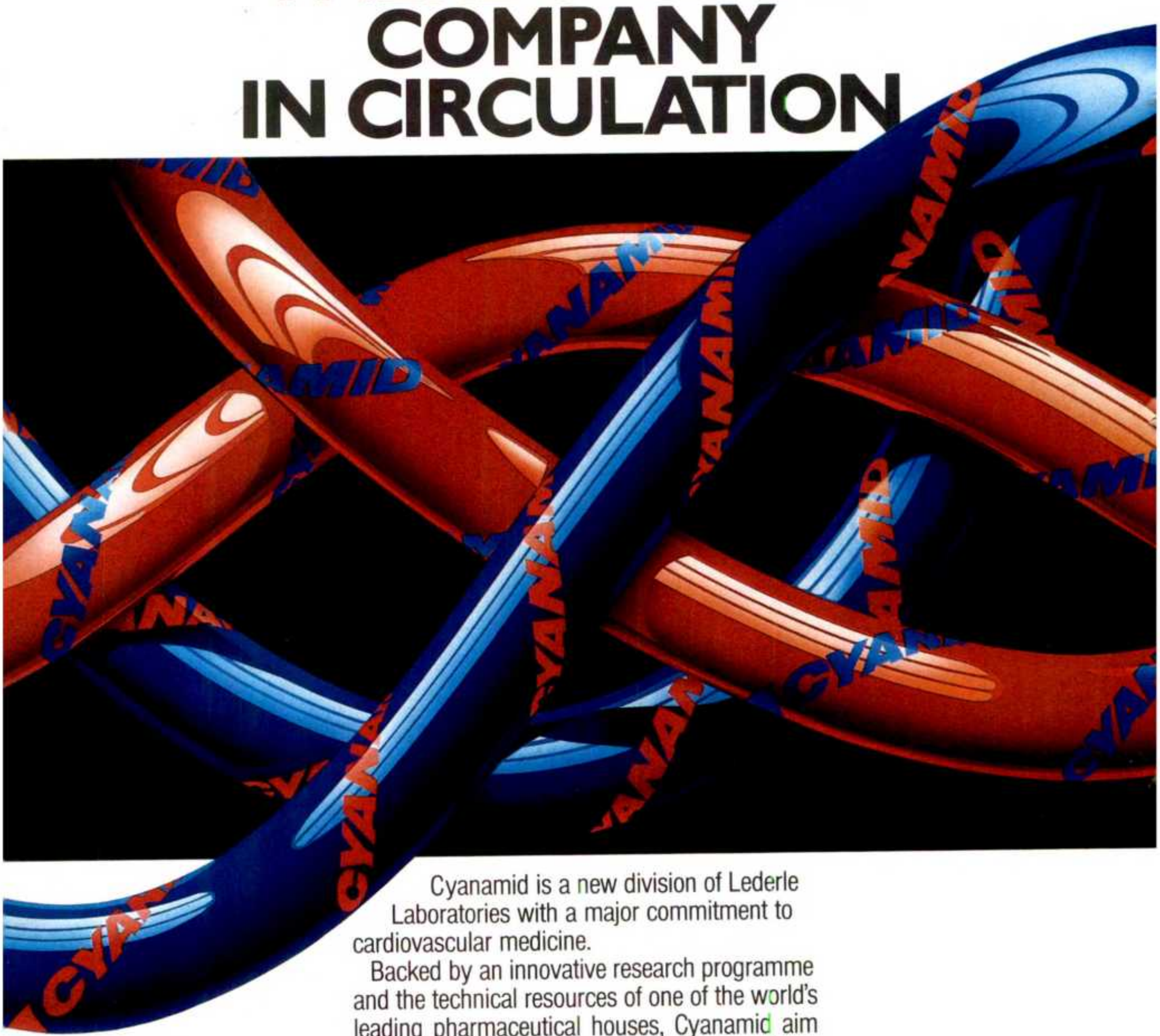

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Randomised crossover trial of rate responsive Activitrax and conventional fixed rate ventricular pacing

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SUMMARY Atrial tracking pacemakers may improve exercise capacity and symptoms because they maintain atrioventricular synchrony and preserve the physiological response of heart rate to exercise. A rate responsive pacemaker which reacts to physical activity may be effective in patients with sinus node disease who are unsuitable for VDD pacing. At least three months after implant a double blind randomised short and long term crossover study was performed in ten patients with complete heart block: block was present at rest and during exercise on a modified Bruce protocol. Symptoms were assessed on a visual analogue scale and exercise capacity (maximal oxygen consumption and anaerobic threshold) was measured during rate responsive (peak rate 125/min) and conventional fixed rate (VVI) pacing (70/min). One month after randomisation treadmill exercise was performed. The mode was then changed to the other pacing mode and exercise was repeated three hours later. After another month the process was repeated but in the reverse order. During long term assessment there was subjective improvement in the sensation of breathlessness with rate responsive pacing. During short term assessment maximal oxygen consumption increased and the benefit was maintained during long term rate responsive compared with long term VVI pacing; oxygen consumption at the anaerobic threshold was similarly improved.

Activity detecting rate responsive pacing is better than fixed rate ventricular pacing in patients with complete atrioventricular block.

Double blind crossover studies have shown that the occurrence or severity of subjective symptoms or both are significantly lower during atrial synchronised ventricular pacing than during fixed rate VVI pacing,[1 2] but there is no agreement about the magnitude of the improvement in exercise capacity. Atrial synchronised ventricular pacing can only ensure a physiological ventricular rate response if the atrial rate is a good indicator of circulatory demand. Patients with sinus bradycardia, sinus arrest, or drug resistant atrial tachycardia are therefore less suitable candidates for atrial synchronised ventricular pacing. The Activitrax pacemaker (Medtronic) varies the pacing rate in response to the level of physical activity as detected by a sensor bonded to the inside of the case of the pulse generator. Recent short term studies have suggested that it was better than fixed rate VVI pacing[3 4] and a multicentre study demonstrated an improvement in exercise duration during Activitrax pacing.[5]

The purpose of this study was to compare the effect of Activitrax rate responsive pacing with that of conventional fixed rate VVI pacing on symptoms and exercise capacity during a randomised short term and long term crossover study. Exercise capacity was assessed by measuring maximal oxygen consumption and anaerobic threshold during treadmill exercise: these measurements are reproducible (coefficient of variation 8%) and seem to provide the most objective indication of exercise capability.[6 7]

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Patients and methods

PATIENT SELECTION

We studied 10 patients (mean age 50 years (range 30–75)) with complete anterograde atrioventricular block at rest and during exercise. Nine patients had retrograde atrioventricular block at rest. Exercise capacity was limited only by dyspnoea or fatigue in all patients. A ventricular rate responsive pacemaker (Activitrax, Medtronic) was implanted in all patients 3–6 months before the start of the study. The underlying cardiac disease was dilated cardiomyopathy (three patients), previous aortic valve surgery (two patients), idiopathic atrioventricular block (two patients), ablation of the atrioventricular node for uncontrolled atrial fibrillation (one patient), hypertension (one patient), and primary pulmonary hypertension with right heart failure (one patient). Patients were excluded from the study if they had suffered a myocardial infarction during the previous six months or had a history suggestive of myocardial ischaemia or pulmonary disease.

TRIAL DESIGN

Treadmill exercise capacity was assessed on a modified Bruce protocol by measuring maximal oxygen consumption and anaerobic threshold by computerised mass spectrometric analysis of mixed expired air.[6] Before entry to the study patients repeated practice exercise tests until symptom limited maximal oxygen consumption differed by less than 5% on two consecutive exercise tests. The exercise tests were performed at the same time of day for each patient. The pacemaker mode was randomised to either fixed rate mode (VVI 70/min) or to rate responsive mode. During the study the patient and the doctor supervising the exercise test were not told what pacemaker mode was being used. In rate responsive mode the back up rate was 70/min and the upper limit was 125/min. The rate response mode and the activity threshold were altered so that during a practice test at maximal exercise capacity the upper rate limit was reached. One month later exercise capacity was assessed in the original randomised mode ("long term mode"). The alternative mode was reprogrammed and the patients re-exercised three hours later ("short term mode"). Similarly, one month later the patient was exercised (alternative long term mode) and re-exercised three hours later in the initial pacing mode (short term mode). Symptoms were assessed at the end of each month of long term mode pacing by a questionnaire completed by the patient. The questionnaire contained 24 questions relevant to the symptoms of breathlessness, fatigue, and psychological state. The questionnaire was developed at McMaster University (available on request from DPL). Each question was on a separate sheet of paper and the patient was requested to make a mark on a visual analogue scale 10 cm in length. The distances of all the marks for each category of questions were summed so that a maximum of 80 indicated maximum symptoms. Left ventricular fractional shortening was assessed by cross sectional echocardiography performed in the VVI mode.

STATISTICAL ANALYSIS

Because data were not normally distributed 95% confidence limits are not quoted. Differences in symptoms and exercise capacity were thus assessed by the Wilcoxon matched pairs rank sum test. Results are quoted as mean and interquartile range (that is the range containing the middle 50% of the sample values).

Results

Mean left ventricular fractional shortening was 28% (range 10–40%, normal 23–37%). Exercise capacity was significantly greater during rate responsive pacing (table 1, figs 1 and 2). During short term assessment the mean maximal oxygen consumption (ml kg/min) increased and the benefit (compared with long term VVI pacing) was maintained during long term rate responsive pacing (18 (1) and 19 (1) *vs* 16 (1) respectively ($p < 0\cdot02$)) This was a mean improvement of 14% (increased, eight patients; unchanged, one patient; decreased, one patient). The anaerobic threshold was reached in seven patients. Oxygen consumption and the anaerobic threshold also improved on rate responsive pacing (14 (1) and 14 (1) *vs* 12 (1) ($p < 0\cdot04$) (increased in six patients, unchanged in one patient). The subjective sensation (out of a maximum score of 80) for symptoms of breathlessness, fatigue, and psychological state were less in rate responsive than in VII pacing, but the difference between the two pacing modes was significant only for the symptom of breathlessness ($p < 0\cdot05$) (eight patients improved, one remained unchanged, and one deteriorated).

Discussion

The problem of impaired exercise capacity associated with chronotropic incompetence has been approached in several ways. Atrial synchronised ventricular pacing reduces the occurrence and severity of subjective symptoms more than fixed rate VVI pacing. The magnitude of the objective improvement is debatable and may reflect the awareness of the pacing mode by the doctor supervising the exercise test.[1 2 8] Improvement in bicycle work-

Table *Measurement of maximal oxygen consumption ($\dot{V}O_2$ max), anaerobic threshold, and visual analogue scale scores (maximum score 80) during short term and long term VVI and rate responsive pacing (VVI-Act)*

			$\dot{V}O_2$ max (ml/kg/min)				*Anaerobic threshold (ml/kg/ml)*				*Visual analogue scale*					
			Long		*Short*		*Long*		*Short*		*SOB*		*Fatigue*		*Psychological*	
Pt No	*Age (yr)*	*Diagnosis*	*VVI-Act*	*VVI*	*VVI-Act*	*VVI*	*VVI-Act*	*VVI*	*VVI-Act*	*VVI*	*VVI-Act*	*VVI*	*VVI-Act*	*VVI*	*VVI-Act*	*VVI*
1	30	PHT	17	14	15	13	15	12	15	13	18	20	33	31	24	26
2	45	IDC	19	17	20	18	15	13	13	12	8	39	38	68	21	13
3	30	AVR	29	24	27	24	16	15	15	15	43	59	45	81	38	51
4	55	Idio	22	17	21	17	16	14	21	17	28	28	8	28	21	30
5	40	AVR	14	12	13	13	11	10	11	10	46	48	52	50	31	24
6	56	ABL	19	16	16	15	NR	NR	NR	NR	55	45	91	76	55	49
7	62	HT	18	16	16	16	NR	NR	NR	NR	15	24	7	9	0	3
8	63	IDC	15	17	18	14	12	12	13	11	25	38	30	41	15	17
9	62	IDC	16	16	17	15	13	12	12	13	18	20	10	11	7	7
10	75	Idio	18	15	18	17	NR	NR	NR	NR	10	63	14	62	12	55
		Mean	18·7*	16·4	18·1*	16·2	14·0†	12·6	14·0‡	13·2	27§	38	33	46	22	28

NR, not reached, $\dot{V}O_2$ max, maximal oxygen consumption; SOB, breathlessness; PHT, pulmonary hypertension; AVR, after aortic valve replacement; Idio, idiopathic, ABL, after atrioventricular node ablation; HT, hypertension; IDC, idiopathic dilated cardiomyopathy

*$p < 0·02$ compared with chronic VVI, †$p < 0·04$ compared with chronic VVI; ‡$p < 0·03$ compared with chronic VVI; §$p < 0·05$ compared with chronic VVI.

load in VDD as compared with VVI mode has been reported as 27[1] and 14%.[2] Some patients may have recognised the pacing mode by feeling their pulse, and this could have influenced the measurement of maximal exercise capacity. Although our patients were not informed of the pacing mode at any time, it was impossible to prevent an intelligent patient from deducing it. To minimise observer bias one physician and a cardiac technician supervised the exercise tests; the physician remained unaware of the pacing mode and the technician observed the electrocardiogram during the test.

Exercise capacity was assessed by measuring maximal oxygen consumption and anaerobic threshold. Assessment of maximal oxygen consumption is precise and reproducible; but it is symptom limited and therefore affected by patient motivation and not totally objective. The physiological meaning of an "anaerobic threshold" is complex but its measurement provides a more objective assessment of exercise capacity.[6 7] Maximal oxygen consumption and anaerobic threshold increased during short term and long term rate responsive pacing. A recent report demonstrated an improvement in maximal oxy-

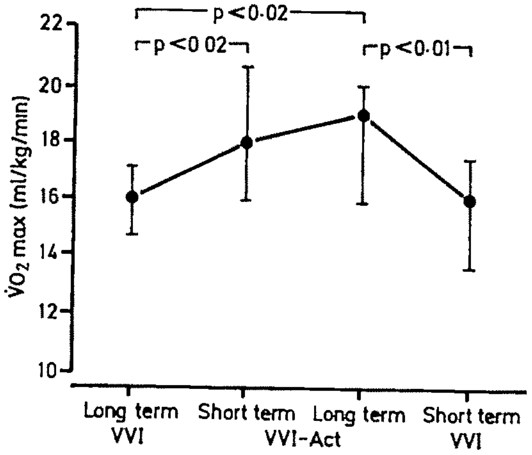

Fig 1 *Changes in maximal oxygen consumption ($\dot{V}O_2$ max) during short term and long term VVI and rate responsive (VVI-Act) pacing. Bars represent interquartile ranges.*

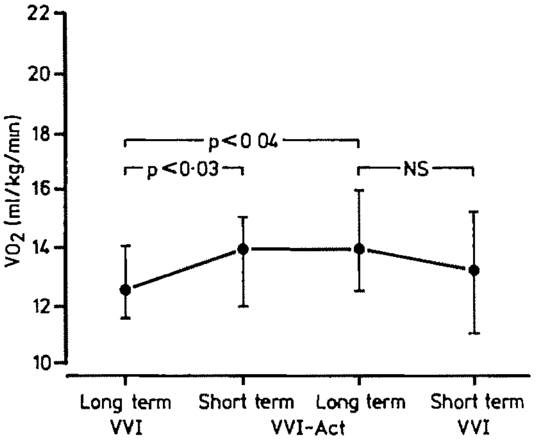

Fig 2 *Changes in anaerobic threshold during acute and chronic VVI and rate responsive (VVI-Act) pacing (7 patients). Bars represent interquartile ranges. $\dot{V}O_2$, oxygen consumption at the anaerobic threshold.*

gen consumption and anaerobic threshold with activity responsive pacing.[4] This short term study included patients in whom there was anterograde conduction through the atrioventricular node during exercise. We excluded such patients from our study because the inherent capacity for a rise in heart rate would have interfered with our objectives. The fact that our patients showed a smaller mean rise in maximal oxygen consumption cannot be explained by this exclusion, but may reflect their older age.

Many patients do not exercise to their maximal capacity and it is reassuring that the present study confirms the impression that subjective symptoms are improved by rate responsive pacing. Rate responsive pacing reduced the symptoms of breathlessness and fatigue, and, interestingly, improved psychological symptoms, though only the effect on the sensation of breathlessness reached statistical significance. Though Humen *et al* demonstrated an improvement in anaerobic threshold but not maximal oxygen consumption in six patients undergoing rate responsive compared with VVI pacing,[9] exercise capacity in their subjects was limited by factors unrelated to cardiovascular performance, such as claudication or arthritis.

Clearly there is an advantage in having an adequate increase in heart rate in response to exercise. A normal atrioventricular sequence may augment cardiac output at rest by about 25%,[10] but during exercise the rate increase may be more important.[8] Haemodynamic function during exercise has been compared in patients during VDD and VVI pacing at a matched heart rate.[11 12] In the first study cardiac output was 8% higher in the VDD mode, whereas in the second study there was no difference between the two modes. As these studies cannot exclude atrioventricular synchrony occurring by chance the role of atrial contribution to the cardiac output response to exercise cannot be fully assessed. We are unaware of any comparison of VDD and rate responsive pacing.

A dual chamber pacemaker is more complex to implant and program than a rate responsive pacemaker and is not suitable for all patients: some may need an alternative form of rate responsiveness pacing. While other sensors can measure the QT interval,[13] respiratory rate,[14] mixed venous oxygen saturation,[15] and pH,[16] we decided to evaluate the activity sensing pacemaker, which also provides a physiological heart rate response to exercise, and offers improved effort tolerance and symptomatic improvement when compared with fixed rate ventricular pacing. It is simple to implant and program, and may sometimes obviate the need for dual chamber pacing, particularly in those patients with atrioventricular block and poorly controlled atrial tachycardias or sinus node disease. Our study demonstrates its advantage over VVI pacing and thus suggests its usefulness in an important proportion of patients with heart block.

We thank Medtronic Inc for financial support.

References

1 Perrins EJ, Morley CA, Chan SL, Sutton R. Randomised controlled trial of physiological and ventricular pacing. *Br Heart J* 1983;50:112–7.

2 Kristensson BE, Arnman K, Smedgard P, Ryden L. Physiological versus single-rate ventricular pacing: a double-blind cross-over study. *PACE* 1985;8:73–84.

3 Ryden L, Smedgard P, Kruse I, Anderson K. Rate responsive pacing by means of activity sensing. *Stimucoeur* 1984;12:181–4.

4 Benditt DG, Mianulli M, Fetter J, *et al.* Single-chamber cardiac pacing with activity initiated chronotropic response: evaluation by cardiopulmonary exercise testing. *Circulation* 1987;75:184–91.

5 Chevalier PA, Murtaugh RA. Rate responsive pacing: improved exercise performance with an activity sensing pacemaker—a multicenter study [Abstract]. *Circulation* 1985;72(suppl III):432.

6 Lipkin DP, Perrins J, Poole-Wilson PA. Respiratory gas exchange in the assessment of patients with impaired ventricular function. *Br Heart J* 1985; 54:321–8.

7 Lipkin DP, Bayliss J, Poole-Wilson PA. The use of a submaximal exercise to predict maximal exercise capacity in patients with heart failure. *Eur Heart J* 1985;6:829–33.

8 Ryden L, Kristensson BE. Rate responsive pacing: effects on hemodynamics, exercise tolerance and subjective feeling of well being. In: Zipes DP, Jalife J, eds. *Cardiac electrophysiology and arrhythmias.* Orlando, Florida: Grune and Stratton, 1985:513–22.

9 Humen DP, Kostuk WJ, Klein GJ. Activity-sensing, rate responsive pacing: improvement in myocardial performance with exercise. *PACE* 1985;8:52–9.

10 Samet P, Bernstein WH, Levine S. Significance of the atrial contribution to ventricular filling. *Am J Cardiol* 1965;16:195–200.

11 Karlof I. Haemodynamic effect of atrial triggered versus fixed rate pacing at rest and during exercise in complete heart block. *Acta Med Scand* 1975; 197:195–206.

12 Ausubel K, Steingart RM, Shimshi M, Klementowicz P, Furman S. Maintenance of exercise stroke volume during ventricular versus atrial synchronous pacing: role of contractility. *Circulation* 1985;72:1037–43.

13 Donaldson RM, Fox KM, Rickards AF. The initial experience with a physiological rate responsive pacemaker. *Br Med J* 1983;286:667–71.

14 Rossi P, Plicchi G, Canducci G, Rognoni G, Aina F. Respiration as a reliable physiological sensor for controlling cardiac pacing rate. *Br Heart J* 1984;51:7–14.

15 Wirtzfeld A, Heinze R, Stanzl K, Hoekstein K, Alt E, Liess HD. Regulation of pacing rate by variations of mixed venous oxygen saturation. *PACE* 1984; 7:1257–62.

16 Contini C, Papeschi G, Ricci D, Strata G, Pauletti M. pH changes in chronic pacemaker pocket. A new means of increasing rate during exercise. Preliminary results [Abstract]. *PACE* 1980;3:366.

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Treatment of angina pectoris with nifedipine: a double blind comparison of nifedipine and slow-release nifedipine alone and in combination with atenolol

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SUMMARY The relative efficacy of nifedipine and slow-release nifedipine (Adalat Retard) in the treatment of stable exertional angina pectoris was evaluated in a double blind randomised crossover study in eight patients on no concomitant antianginal treatment and in 10 patients who were additionally on atenolol. Patients were assessed by angina diaries and exercise testing. Slow-release nifedipine was as effective as nifedipine in the treatment of these patients, both alone and in combination with atenolol.

Nifedipine is well established in the treatment of stable exertional angina pectoris both alone[1] and in combination with β receptor antagonists.[2] A slow-release nifedipine preparation (20 mg tablets) is now available for the treatment of hypertension and twice daily administration of this preparation is as effective as a daily dose of 30 mg (one 10 mg capsule three times a day) of the short acting preparation.[3] This is clearly more convenient for the patient and it may also avoid the high peak post-dose concentrations of nifedipine which may contribute to side effects[4] and limit its usefulness. Slow-release nifedipine (Adalat Retard) is therefore being increasingly prescribed for the treatment of exertional angina despite any evidence to show that it is effective in this situation. In this study we have compared the two preparations of nifedipine both alone and in combination with a β receptor antagonist in the treatment of stable exertional angina.

Patients and methods

We studied two groups of patients. All were normotensive and had stable (>3 months) exertional angina pectoris. All had important atheromatous coronary artery disease demonstrated on coronary arteriography. None had suffered a myocardial infarction within the previous year, none had heart failure or respiratory disease, and none was taking digoxin or antiarrhythmic agents. Group 1 consisted of eight patients (seven men and one woman, mean (SEM) age 58 (7) years) and group 2 consisted of 10 patients (nine men and one woman, mean (SEM) age 54 (6) years). Group 1 patients were on no other treatment whereas group 2 patients were taking a β_1 receptor antagonist (atenolol 100 mg daily). Before entering the study all had chest pain and significant ST segment depression on treadmill exercise testing. Significant ST segment depression was defined as planar or downsloping depression of >1 mm occurring 0·08 seconds after the J point. The study consisted of a two week single blind placebo run in period followed by two treatment phases each lasting two weeks during which the patients received either nifedipine or slow-release nifedipine in a double blind randomised crossover manner. Nifedipine was given in a dose of 10 mg three times daily for the first three days and then 20 mg three times daily for the remainder of that phase to avoid the problems that occasionally arise from administering the higher dose.[1] For the same reason slow-release nifedipine was started in a dose of 20 mg twice daily for three days and thereafter increased to 40 mg twice daily. Throughout the study patients were encouraged to undertake their normal activities and used sublingual nitroglycerin for pain relief.

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To assess the effects of treatment we used the angina diaries that the patients kept throughout the placebo run in period and the two treatment periods and the maximum symptom limited treadmill exercise tests that they performed at the end of each two week period. A standard 12 lead electrocardiogram was recorded before and at one minute intervals during exercise together with heart rate and blood pressure. Exercise tests were terminated by severe chest pain, hypotension, arrhythmias, exhaustion, and when >3 mm ST segment depression occurred with or without pain. The duration of exercise to chest pain, 1 mm ST segment depression, and maximum exercise were noted.

Results are expressed as mean (SEM) and data were compared by Student's *t* test for paired observations.

Results

GROUP 1: NIFEDIPINE VERSUS SLOW-RELEASE NIFEDIPINE ALONE

Angina frequency was similar during the placebo period and during the two treatment phases of the study (table 1). No patient reported symptomatic deterioration with either nifedipine preparation. Heart rate and rate pressure product at rest and at 1 mm ST segment depression were similar with the two preparations of nifedipine (table 2). Exercise duration to pain and to 1 mm ST segment depression and maximum exercise duration were significantly prolonged by both nifedipine and slow-release nifedipine compared with the placebo but there was no difference between either preparation (table 1 and figure). Responses to the two preparations varied: in three patients exercise duration to 1 mm ST segment depression was greater with slow-release nifedipine than with nifedipine, in four it was similar, and in one patient it was greater with nifedipine than with slow-release nifedipine (figure).

GROUP 2: NIFEDIPINE VERSUS SLOW-RELEASE NIFEDIPINE IN COMBINATION WITH ATENOLOL

Results were similar in this group of patients. Angina frequency tended to be less during treatment with slow-release nifedipine than with nifedipine

Table 1 *Angina frequency and duration of treadmill exercise to 1 mm ST segment depression, to chest pain, and to the termination of the test in both patient groups during the placebo run in period and the two treatment phases of the study (mean (SEM))*

		Duration of exercise (min) to:		
	Angina frequency (episodes/week)	*1 mm ST segment depression*	*Chest pain*	*Termination of test*
Group 1				
Placebo	6·1 (3·5)	4·5 (0·8)	6·0 (0·9)	6·9 (0·7)
Nifedipine	5·5 (4·0)	5·8 (0·9)*	8·9 (0·9)*	9·4 (0·6)*
Slow-release nifedipine	5·3 (4·0)	6·3 (1·1)*	7·8 (0·9)*	8·7 (0·8)*
Group 2				
Placebo	7·8 (3·4)	5·6 (0·8)	6·2 (0·5)	7·8 (0·7)
Nifedipine	7·3 (2·9)	6·2 (0·9)	6·7 (0·7)	8·1 (0·6)
Slow-release nifedipine	5·5 (1·9)	6·5 (0·8)	6·7 (0·8)	8·4 (0·8)

*p < 0·01 compared with placebo.

Table 2 *Haemodynamic function (mean (SEM)) at rest and during treadmill exercise at 1 mm ST segment depression*

	At rest		*At 1 mm ST segment depression*	
	Heart rate (beats/min)	*Rate pressure product*	*Heart rate (beats/min)*	*Rate pressure product*
Group 1				
Placebo	70 (4)	10170 (2116)	111 (10)	20838 (1833)
Nifedipine	73 (5)	10376 (2261)	114 (9)	21078 (1998)
Slow-release nifedipine	77 (5)	11207 (1038)	126 (10)	22139 (1643)
Group 2				
Placebo	50 (1)	6777 (251)	89 (5)	15427 (1093)
Nifedipine	56 (2)	7601 (293)	91 (5)	16160 (1260)
Slow-release nifedipine	56 (2)	7788 (383)	90 (5)	15917 (1167)

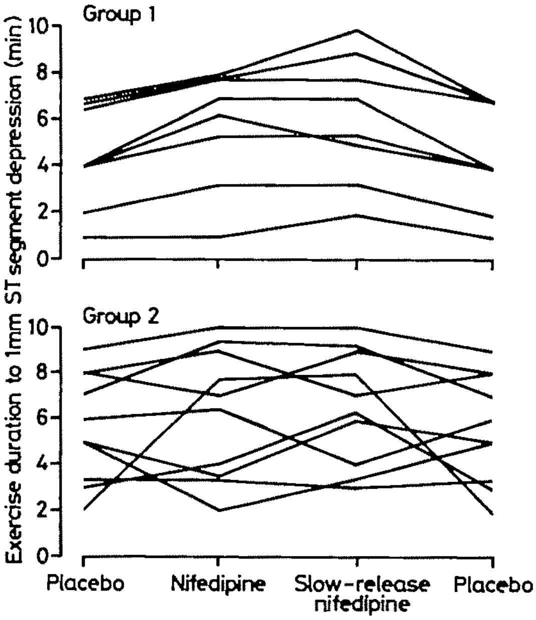

Figure *Exercise duration to 1 mm ST segment depression during the placebo run in period and the two treatment periods in groups 1 and 2. Individual patient responses are shown.*

and the placebo run in period but the differences were not significant (table 1). As in group 1, heart rate and rate pressure product at rest and at 1 mm ST segment depression were similar on the two preparations (table 2). When the results of exercise testing were examined in the group as a whole, addition of nifedipine or slow-release nifedipine to atenolol did not prolong the duration of exercise to 1 mm ST segment depression or to pain or the maximum exercise duration (table 1 and figure).

Individual patients responded differently to both nifedipine preparations. Addition of nifedipine to atenolol improved exercise duration to 1 mm ST segment depression in six patients; no change occurred in one and there was a deterioration in three (figure). Addition of slow-release nifedipine to atenolol produced an improvement in exercise duration to 1 mm ST segment depression in six patients and a deterioration in three (figure). Four patients exercised for longer before the onset of ST segment depression on slow-release nifedipine than on nifedipine, two exercised for longer on nifedipine, and in four patients the exercise durations were similar on both preparations (figure).

Two patients complained of ankle oedema on nifedipine and one on slow-release nifedipine. Two patients experienced facial flushing and one transient lightheadedness after nifedipine.

Discussion

The patients in this study all had angina on effort and none gave a history of rest pain. This suggests that coronary flow limitation due to obstructive coronary artery disease was the cause of their symptoms rather than a change in vasomotor tone. Nifedipine is a calcium channel blocking agent with no important negative inotropic effects.[5] It is a smooth muscle relaxant causing not only peripheral arteriolar dilatation but also coronary vasodilatation.[6] Several studies have shown it to be an effective antianginal agent in patients with exertional angina, improving exercise haemodynamics and pain frequency both alone[1] and in combination with a β blocker.[2] In one study a variable response to nifedipine was found; although some patients improved at a dose of 30 mg a day they became worse at higher doses.[1] To avoid this, all patients in this study were started on the lower dose of nifedipine or slow-release nifedipine and after three days the higher dose was given. All of our patients were able to continue on the higher dose.

Slow-release nifedipine is now being used to treat angina caused by obstructive coronary artery disease on the assumption that because the short acting preparation is effective a long acting preparation will be equally effective. This is not necessarily true and some preliminary unpublished data have suggested that slow-release nifedipine may not be effective in angina. Consequently, the manufacturers of the preparation have not been promoting its use in angina. The present study suggests that the slow-release preparation is as effective as the short acting preparation in angina both alone and in combination with a β blocker and that the blood concentrations obtained with the slow-release preparation are adequate.

Previous studies have shown a synergistic effect between nifedipine and a β blocker.[2] Theoretically, this would be expected since the detrimental effects of both drugs such as tachycardia induced by nifedipine will be prevented by the β blocker and any increase in vascular resistance induced by the β blocker will be overcome by nifedipine. Consequently, these two groups of drugs are widely used in combination. We therefore investigated the efficacy of slow-release nifedipine not only compared with nifedipine alone but also in combination with a β blocker, atenolol. In this study the addition of nifedipine or slow-release nifedipine to atenolol produced no further benefit in the group as a whole in terms of angina frequency or exercise testing, though individual patients did improve—six with nifedipine and six with slow-release nifedipine. This is contrary to the findings of an earlier study in which the combination of nifedipine and propranolol was more effective than either drug alone.[2] A possible explanation for the difference between our results with atenolol and those with propranolol may be due to the selectivity of the β receptor blockade. Atenolol is a highly selective β_1 antagonist, whereas propranolol is a relatively non-selective β receptor antagonist. Thus the undesirable effects of β blockade, in particular the effects caused by β_2 receptor antagonism, such as a rise in peripheral or coronary vascular resistance, may have been less with atenolol than with propranolol and so any potential beneficial effects of a vasodilator may have been reduced. Findlay *et al* investigated the effects of nifedipine and atenolol both alone and in combination in the treatment of stable exertional angina pectoris and found that the combination was more effective than either drug alone when compared with placebo[7] but they did not compare the combination with atenolol alone. A recent study in which the effects of verapamil, another calcium antagonist, and atenolol were compared both alone and in combination showed that the combination of the two drugs was more effective than either drug alone in improving exercise duration.[8] Again this differs from our results and it may be because verapamil has greater negative inotropic effects than nifedipine. These will reduce myocardial work even further and hence energy and oxygen demands.

Though there was no difference between the preparations in the groups as a whole, individual patient responses were variable. Examination of these results shows that individual patients in both groups responded better to one preparation than the other in terms of exercise duration to 1 mm ST segment depression. This may reflect a similar phenomenon to that described previously in which a variation in the individual response to the short acting nifedipine was found.[1] Thus if an unsatisfactory response is obtained in one patient it may be worthwhile trying the alternative preparation.

Slow-release nifedipine is an effective alternative to the more usual capsular preparation in the treatment of angina pectoris and could be used as the initial treatment in place of the capsular form alone or in combination with a β blocker.

References

1 Deanfield J, Wright C, Fox K. Treatment of angina pectoris with nifedipine: the importance of dose titration. *Br Med J* 1983;286:1467–70.

2 Lynch P, Dargie H, Krikler S, Krikler D. Objective assessment of antianginal treatment: a double blind comparison of propranolol, nifedipine and their combination. *Br Med J* 1980;280:184–7.

3 Boneduce D, Canonico V, Mazza F, *et al.* Evaluation of the efficacy of slow-release nifedipine in systemic hypertension by ambulatory intra-arterial blood pressure monitoring. *J Cardiovasc Pharmacol* 1985;7:145–51.

4 Zylber-Katz E, Koren G, Granit L, Levy M. Bioavailability of nifedipine. Comparison between two preparations. *Biopharm Drug Dispos* 1984;5:109–15

5 Antman EM, Stone PH, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part 1. basic and clinical electrophysiologic effects *Ann Intern Med* 1980;93:875–85.

6 Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers and vascular smooth muscle. *Annu Rev Pharmacol Toxicol* 1977;7:149–66.

7 Findlay IN, MacLeod K, Ford M, Gillen G, Elliott AT, Dargie HJ. Treatment of angina pectoris with nifedipine and atenolol: efficacy and effect on cardiac function. *Br Heart J* 1986;55:240–5

8 Findlay IN, MacLeod K, Gillen G, Elliott AT, Aitchison T, Dargie HJ. A double blind placebo controlled comparison of verapamil, atenolol, and their combination in patients with chronic stable angina pectoris. *Br Heart J* 1987;57:336–43.

Br Heart J 1987;58:621–6

Magnetic resonance imaging of the pulmonary arteries and their systemic connections in pulmonary atresia: comparison with angiographic and surgical findings

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SUMMARY Patients with pulmonary atresia require several investigations and operations. The role of magnetic resonance imaging in assessing the anatomy of the central pulmonary arteries, the origin and course of systemic collateral arteries, and the patency of surgical shunts has been studied with the aim of reducing the need for invasive angiography. Transverse, coronal, and sagittal images were obtained in ten adult patients and assessed without knowledge of surgical and angiographic data. Central pulmonary artery anatomy varied from full development to complete absence. Transverse slices showed hypoplastic arteries particularly well and the findings accorded with surgical and angiographic data in all patients. The origin and proximal course of 15 large collaterals were identified on the magnetic resonance images and 18 were identified by surgical and angiographic data. Magnetic resonance imaging did not show their distal connections; if such information is required angiography will be needed. Five surgical shunts were shown to be patent and two occluded at surgery and angiography, and this was confirmed on the magnetic resonance images. The patency of a further four shunts was uncertain, but they were not seen by magnetic resonance and were presumed to be occluded.

Patients with pulmonary atresia depend upon branches of the systemic circulation to provide a pulmonary blood supply. Development of pulmonary arteries centrally and segmentally is variable, as is the size and number of the systemic collateral arteries, and there tends to be an inverse relation between the two.[1] Successful palliative or radical reparative surgery depends on complete demonstration of both, and currently this information cannot be obtained non-invasively, but requires angiography with multiple contrast injections and selective catheterisation of individual collateral arteries.[2-4] It is also important to establish the state of surgical shunts.[5]

The role of magnetic resonance imaging in assessing the anatomy of the central pulmonary arteries, the origin and course of systemic collateral arteries, and the patency of surgical shunts has been studied and compared with angiographic and surgical findings with the ultimate aim of reducing the need for invasive investigation.

Patients and methods

We studied 10 adult patients (seven men and three women aged 19–40 (mean 24)). We chose to study adults because sedation was not used and it was essential for the patients to lie still during the acquisition of the images. Eight had a subaortic ventricular septal defect with normal atrioventricular connections. Two had abnormal atrioventricular connections. Up to the time of the study a total of 39 angiographic investigations and 13 operations had

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been performed in the 10 patients (table).

The magnetic resonance images were acquired with a Picker International Vista MR2055 machine with a superconducting magnet operating at 0·5 T. A spin echo sequence (echo time 40 ms) was used, and the radiofrequency signals were received with specially constructed thoracic surface coils. Images were acquired in transverse, coronal, and sagittal planes through the area of interest. Six or eight 1 cm thick tomographic slices were obtained simultaneously with electrocardiographic gating. Where indicated these were repeated with an offset of 0·5 cm to give an interleaved set of 1 cm thick slices 0·5 cm apart. The pixel size was 1·2 mm × 1·2 mm and each group of slices was obtained over 256 cardiac cycles, consisting of two acquisitions for each of 128 phase encoding steps. In order to maximise the contrast between moving blood and soft tissue, data acquisition was concentrated into the systolic period, and by use of the minimum repeat time it was possible to acquire eight slices within 560 ms of

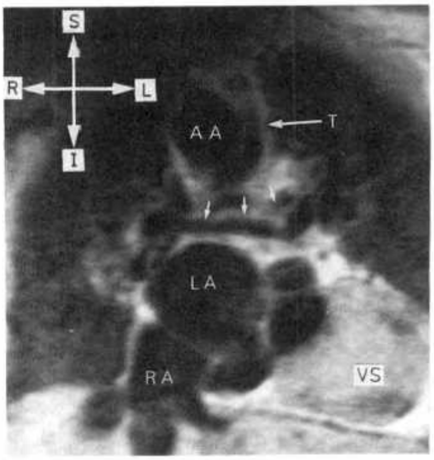

Fig 1 *Magnetic resonance image of coronal slice in patient 8 showing hypoplastic central pulmonary arteries (arrows). The aortic arch (AA) is to the right. LA, left atrium; RA, right atrium; T, trachea; VS, ventricular septum.*

Table *Data on patients*

				Angiography	
Patient No	*Age (yr)*	*Sex*	*Diagnosis*	*Date*	*Findings*
1	28	M	Pulmonary atresia, tricuspid atresia	1964	
				1970	
				1976	
				1977	LPA seen
				1979	Small RPA, no LPA
				1982	Shunt blocked, multiple collaterals
				1985	No PAs seen
2	23	M	Pulmonary atresia, VSD	1965	
				1974	4 collaterals from descending aorta
				1978	Small central PAs
				1980	Patent shunt
3	22	M	Pulmonary atresia, VSD	1966	
				1969	3 collaterals: no PAs seen
				1976	2 collaterals: no PAs
				1978	LPA seen
				1985	No shunt seen
4	22	M	Pulmonary atresia, VSD	1965	No PAs seen
				1975	
				1981	Patent shunt
				1986	Patent shunt: small RPA: 1 collateral on right
5	19	M	Pulmonary atresia, TAPVD, single atrium, single ventricle	1969	
				1978	
				1983	No PAs seen
				1984	
6	19	M	Pulmonary atresia, VSD	1969	
				1974	Multiple small collaterals: no PAs seen
				1977	Small central PAs
				1980	Confluent PAs
				1984	Both shunts patent: 1 collateral on right
7	19	M	Pulmonary atresia, VSD	1971	
				1976	No PAs
				1979	2 collaterals to left, 1 collateral to right
8	40	F	Pulmonary atresia, VSD	1945	
				1984	Collaterals to right and left: PAs not seen
				1984	1 collateral to left, 2 collaterals to right, small confluent PAs
9	28	F	Fallot: acquired pulmonary atresia	1963	Confluent PAs, no collaterals seen
10	19	F	Pulmonary atresia, VSD	1966	
				1972	No PAs seen, 1 collateral
				1981	2 collaterals to right, 1 collateral to left

Ao, aorta; collateral, systemic-pulmonary collateral artery; L, left; PA, pulmonary artery; PT, pulmonary trunk; R, right; SA, subclavian artery; TAPVD, total anomalous pulmonary venous drainage; VSD, ventricular septal defect.

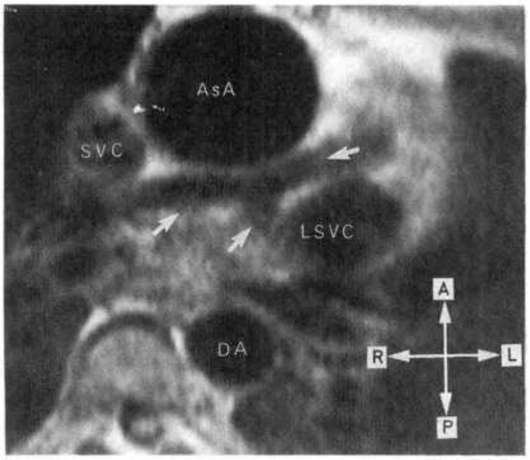

Fig 2 *Magnetic resonance image of transverse slice in patient 6 showing hypoplastic central pulmonary arteries (arrows). AsA, ascending aorta; SVC, superior vena cava; LSVC, left superior vena cava; DA, descending aorta.*

the R wave. The magnetic resonance images were interpreted without knowledge of the other findings and were subsequently compared with the most recent angiographic and surgical data.

Results

The table summarises the results. Confluent pulmonary arteries were seen on the magnetic resonance images in six patients (figs 1 and 2). They could be readily identified from their shape and position in the mediastinum. In five the picture accorded with the angiographic and surgical findings. In the sixth (patient 5) no central pulmonary arteries were seen at angiography or surgery, but they could have been missed owing to their small size.

A total of 15 collateral origins from the descending aorta could be identified on the magnetic resonance images compared with 18 on angiography (figs 3 and 4). Two were missed in patient 10, but the images were technically inadequate. It was possible to fol-

Surgery				
Date	*Findings*	*Procedure*	*Magnetic resonance*	*Patient No*
				1
1972		Attempted Ao-RPA shunt	Small LPA, no RPA	
1979	LPA 5 mm	Duramater Ao-LPA shunt	No collaterals	
1982	LPA and shunt block	Exploration LPA	No shunt seen	
			Confluent PAs	2
			2 collaterals to left	
			1 collateral to right and left	
1979	Small confluent PAs	Ao-PT direct shunt	Ao-PA shunt patent	
				3
			Confluent PAs	
			1 collateral to right	
			1 collateral to left	
1969	2·5 mm left hilar vessel	Left Ao-collateral shunt	No shunt seen	
				4
			Large LPA: small RPA	
			No collaterals	
1965	Small LPA	Left Blalock shunt	Patent shunt	
				5
			Confluent PAs	
			1 collateral to right	
1984	No PAs: 2 collaterals to right	RSA-collateral shunt	No shunt seen	
				6
			Confluent PAs	
1978	RPA present	Right Blalock shunt	1 collateral (?) side	
1982	LPA 5 mm	Left Blalock shunt	Patent shunts	
			No PAs seen	7
			3 collaterals to left, 1 collateral to right	
1978	3 mm right hilar vessel	Right Ao-collateral shunt	Patent shunt	
			Confluent PAs	8
			2 collaterals to left	
	Confluent PAs,		1 collateral to right	
1984	LPA 3 mm, RPA 2 mm	Ao-confluence shunt	No shunt seen	
			Confluent PAs. No collaterals	9
1963	RPA present	Left Blalock shunt	No shunt seen	10
			Non-confluent PAs	
1981	LPA 5 mm, 2 collaterals to left	Left Blalock shunt	1 collateral to left	

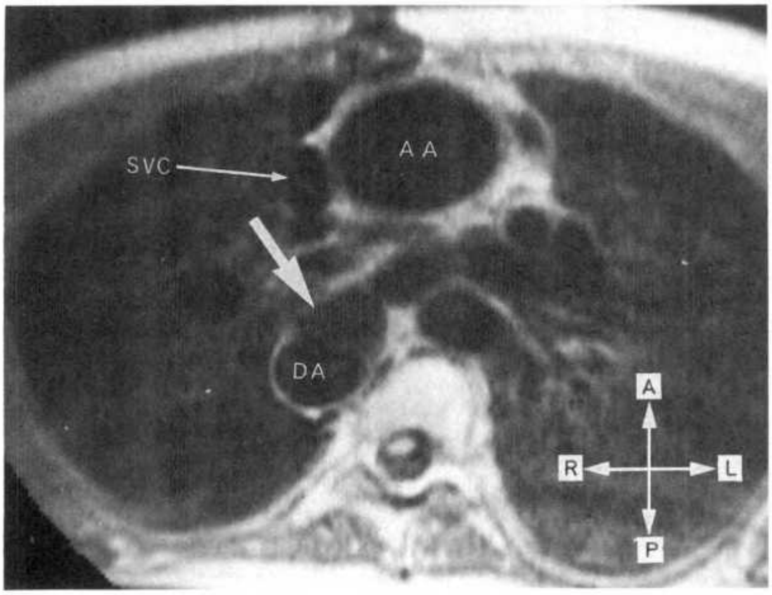

Fig 3 *Magnetic resonance image of transverse slice in patient 8 showing origin of systemic-pulmonary collateral (arrow) from descending aorta which is of a similar diameter. The vessel has a stenosis and passes to the left hilum. SVC, superior vena cava; AA, ascending aorta; DA, descending aorta.*

low the course of most of the collaterals to the hilum, but not possible to establish their distal connections and interconnections. This is in contrast with selective angiography where such information can usually be obtained.

The magnetic resonance images and angiographic and surgical findings showed that five of the 11 surgical shunts were patent and two were blocked (figs 5 and 6). The state of the other four shunts on the angiograms was uncertain, but as they were not seen on the magnetic resonance images they were assumed to be occluded.

Discussion

Many patients with pulmonary atresia who survive into adult life have undergone multiple investigations and operations, like the ten patients in this study. At catheterisation there are practical problems in providing a complete angiographic assessment. Aortic flow is usually high so that aortography alone is inadequate. Selective catheterisation is necessary and failure to intubate all the branches is common, so that even in the first instance more than one investigation may be required to demonstrate the complete anatomy.[6] The vital information is the size and connections of the central pulmonary arteries, which may be difficult to see on angiography as they are rarely connected directly to the aorta and fill only by retrograde flow.[7] In some instances pulmonary venous wedge angiography may be necessary to demonstrate them.[8] These vessels could be easily identified on the magnetic resonance images from their resemblance to a seagull in flight and their position in the mediastinum.[3]

In contrast, the number of origins of collateral arteries arising from the descending aorta were underestimated on the magnetic resonance images; this may be because it is difficult to be certain about the number of origins from the aorta on selective angiography, as an early bifurcation may lead to an overestimation. Beyond the origin of these vessels, it

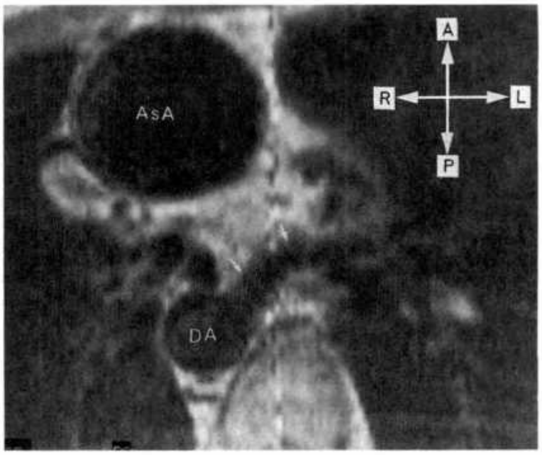

Fig 4 *Magnetic resonance image of transverse slice in patient 3 showing origin of systemic-pulmonary collateral (arrows) from descending aorta (DA) passing to left hilum. AsA, ascending aorta.*

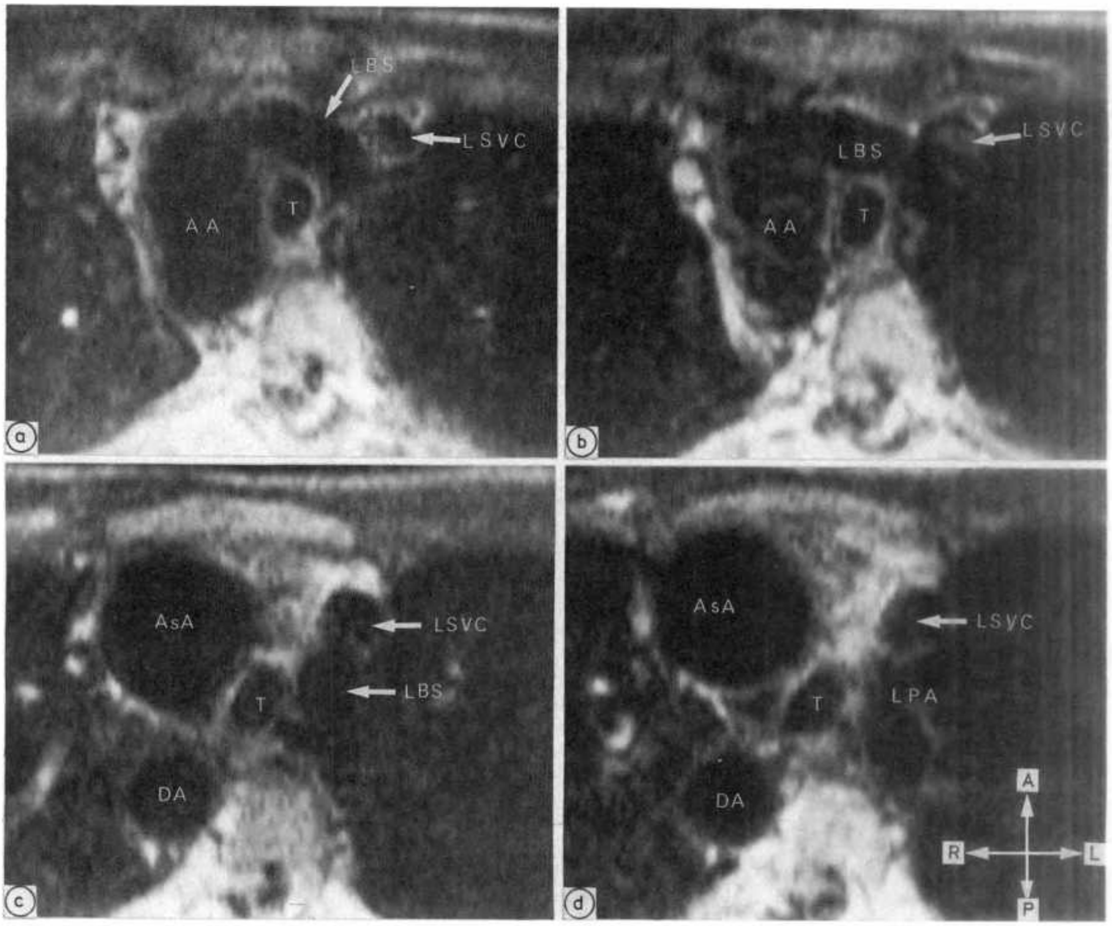

Fig 5 *Magnetic resonance images of contiguous transverse slices (a–d) in patient 5 showing widely patent left Blalock shunt (LBS). Slice a is cranial at the level of the aortic arch and slice d caudal through the hilar region. AA, aortic arch; AsA, ascending aorta; DA, descending aorta; LSVC, left superior vena cava; T, trachea; LPA, left pulmonary artery.*

was possible in most instances to follow them to the hilum but not possible to establish their distal vascular connections. This information is of importance when planning operation, as the number of segments in the lungs to which the true pulmonary arteries, as opposed to collateral arteries only, are connected is an important determinant of prognosis.[9-11] Selective angiography remains the only method of demonstrating such connections and therefore will still be required for this purpose.

There was good agreement between the magnetic resonance and the angiographic and surgical findings on the state of surgical shunts. In those four patients in whom the state of the shunt was uncertain from the angiographic data, failure to visualise a patent shunt by magnetic resonance was an indication that the shunt was likely to be occluded.

Magnetic resonance imaging in pulmonary atresia provides an alternative non-invasive method of obtaining much of the anatomical information required to plan surgical treatment and should reduce the need for invasive angiography in these patients.

References

1 Jefferson K, Rees S, Somerville J. Systemic arterial supply to the lungs in pulmonary atresia and its relation to pulmonary artery development. *Br Heart J* 1972;**34**:418–27.
2 Somerville J. Management of pulmonary atresia. *Br*

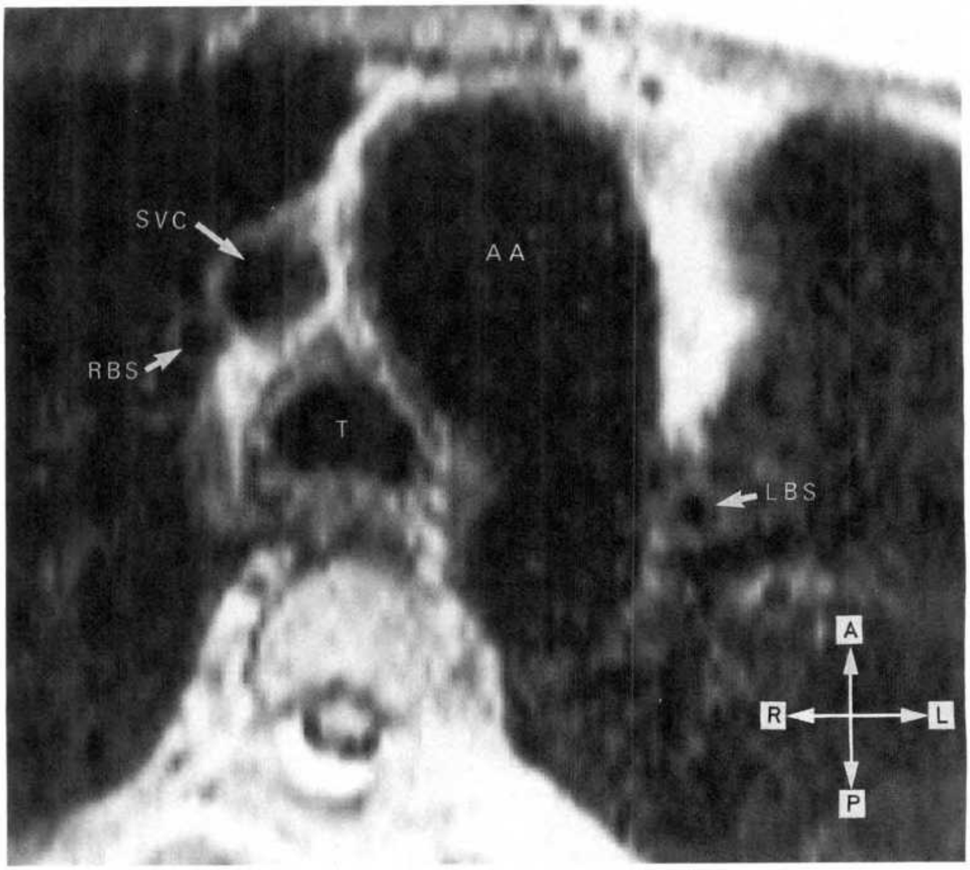

Fig 6 *Magnetic resonance image of transverse slice in patient 6 through aortic arch (AA) showing patent right (RBS) and left (LBS) Blalock shunts. SVC, superior vena cava: T, trachea.*

Heart J 1970;**32**:641–51.

3 Somerville J, Saravalli O, Ross D. Complex pulmonary atresia with congenital systemic collaterals: classification and management. *Arch Mal Coeur* 1978;**71**:322–8.

4 Chesler E, Beck W, Shrire V. Selective catheterization of pulmonary or bronchial arteries in the preoperative assessment of pseudo-truncus arteriosus type IV. *Am J Cardiol* 1970;**26**:20–4.

5 Jacobstein MD, Fletcher BD, Nelson AD, *et al.* Magnetic resonance imaging: evaluation of palliative systemic-pulmonary shunts. *Circulation* 1984;**70**: 650–6.

6 Davis GD, Fulton RE, Ritter DG, *et al.* Congenital pulmonary atresia with ventricular septal defect: angiographic and surgical correlates. *Radiology* 1978; **128**:133–44.

7 Fulton RE, Davis GD. Congenital pulmonary atresia: photographic subtraction as an aid in recognizing hypoplastic pulmonary arteries. *AJR* 1978; **131**:1003–7.

8 Nihill MR, Mullins CE, McNamara DG. Visualization of pulmonary arteries in pseudotruncus by pulmonary vein wedge angiography. *Circulation* 1978;**58**:140–7.

9 Fäller K, Haworth SG, Taylor JFN, Macartney FJ. Duplicate sources of pulmonary blood supply in pulmonary atresia with ventricular septal defect. *Br Heart J* 1981;**46**:263–8.

10 Haworth SG, Macartney FJ. Growth and development of pulmonary circulation in pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. *Br Heart J* 1980;**44**:14–24.

11 Pacifico AD, Allen RH, Colvin EV. Direct reconstruction of pulmonary artery arborization anomaly and intracardiac repair of pulmonary atresia with ventricular septal defect. *Am J Cardiol* 1985;**55**: 1647–9.

Br Heart J 1987;**58**:627–34

Cross sectional echocardiographic assessment of great artery diameters in infants and children

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SUMMARY The pulmonary trunk and aortic root were measured on cross sectional echocardiograms in 173 normal subjects aged from one day to 15 years. Fifteen neonates were re-examined 3–6 days later. The great vessels were visualised in the parasternal long axis and short axis views. All measurements were made in end diastole and end systole by the leading edge method. The internal diameter (inner surface to inner surface) of the pulmonary trunk was also measured. The diameters of the great vessels correlated best with the square root of body surface area. Individual variability in cardiac growth gave a wide scatter of normal values. This was controlled for by calculating the ratio of the pulmonary trunk to aortic root for each subject. This ratio showed little individual variability and, except for the neonatal period, was remarkably constant throughout infancy and childhood (1·06 (0·06)). In the first 24 hours of life the ratio of the pulmonary trunk to the aortic root was significantly larger (1·29 (0·12)) but within one week it decreased to the "normal" ratio found in the older age groups.

These normal data should be useful in assessing patients with congenital heart disease, particularly those in whom pulmonary blood flow is abnormal.

Congenital heart disease is often associated with increased or decreased pulmonary artery blood flow or blood pressure. The relation between pulmonary artery diameter and pulmonary flow or pressure has been evaluated in pathological,[1 2] angiocardiographic[3 4] and, more recently, echocardiographic studies.[5 6] In children with a left to right shunt excellent correlations have been found between shunt size and pulmonary artery diameter on cross sectional echocardiograms, particularly when pulmonary artery size was related to the diameter of the aortic root.[5 7] In patients with decreased pulmonary flow, as in tetralogy of Fallot, the diameter of the pulmonary artery has been used as an important criterion for selecting patients for total correction.[8]

Few cross sectional echocardiographic data are available on the normal values of pulmonary trunk and aortic root size in children.[5-7] Some results are controversial because of the echocardiographic view and measuring techniques that were chosen. To provide normal values through a wide range of ages and body surface areas, we measured the diameter of the great vessels in a large group of neonates, infants, and children and we analysed some variables which might influence these measurements. We also did repeat studies on a subgroup of 15 neonates to determine the changes that occurred in the first week of life.

Patients and methods

We studied 173 children (97 boys and 76 girls) in whom good quality cross sectional echocardiograms were obtained. Physical examination, an electrocardiogram, and the echocardiogram itself helped to exclude cardiac disease. Patients with respiratory disorders, severe anaemia, a febrile illness, or a disease known to alter cardiac function were excluded. Two groups of subjects were evaluated.

Group 1 consisted of 20 normal neonates from the Maternity Hospital. Mean (1 SD) gestational age

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was 39·5 (0·9) weeks and mean weight was 3·41 (0·30) kg. This group was further subdivided according to age. Subgroup 1A was 10 neonates examined within 12 hours of birth and subgroup 1B 10 neonates examined between 12 and 24 hours of life. Fifteen of these 20 infants were restudied 3–6 days after the initial examination.

Group 2 consisted of 153 infants and children, aged one week to 15 years (mean 4·4 years). They were taken at random from the outpatient or inpatient services of the hospital or were the children of employees of the hospital or medical school. In selecting subjects we tried to obtain a more or less equal distribution across the age groups and range of body surface area. Weight and height were reported at the time of echocardiography. The body surface area was calculated by the Boothby and Sandiford modification of the Dubois nomogram.[9]

ECHOCARDIOGRAPHIC STUDIES

Cross sectional echocardiographic examinations were performed with an ATL/ADR mechanical sector scanner with 3·5 or 5 MHz focused transducers. The instrument had built-in movable electronic callipers which automatically calculated the distance between two points. All diameters were directly measured on the video screen of the scanner. The subjects were examined in the supine or left lateral decubitus position. The pulmonary artery was imaged in the parasternal right ventricular long axis view. This section allows good visualisation of the entire right ventricular outflow region, the pulmonary valve, and the pulmonary trunk. The diameter of the pulmonary trunk was measured at the pulmonary valve level (fig 1a). The aortic root diameter was imaged in the parasternal left ventricular long axis view and its diameter was measured distal to the sinuses of Valsalva (fig 1b). In addition, both great arteries were imaged simultaneously in the parasternal short axis view. In this instance the diameters of the pulmonary trunk and aortic root were measured at valve level.

Measurements were made by the leading edge method. This technique could not always be applied reliably to the pulmonary artery imaged in the parasternal short axis view. For comparison we used both methods (leading edge and inner to inner surface) to measure the pulmonary trunk in the parasternal long axis view. All measurements were obtained in both end diastole (at the onset of QRS) and end systole (at the onset of the T wave). We took the mean value of three measurements. We also calculated the ratio of the pulmonary trunk to the aortic root in end systole and end diastole.

STATISTICAL ANALYSIS

We used a regression mode to express each echo measurement as a function of body surface area. In a preliminary evaluation the echo measurements were analysed as linear, logarithmic, square root, and cube root functions of body surface area. The function that had the smallest residual sum of squares and the highest correlation coefficient was used in the final regression equation. The pulmonary trunk to aortic root ratio was determined from the parasternal long axis and short axis views and analysed as a linear function of the body surface area (table 1).

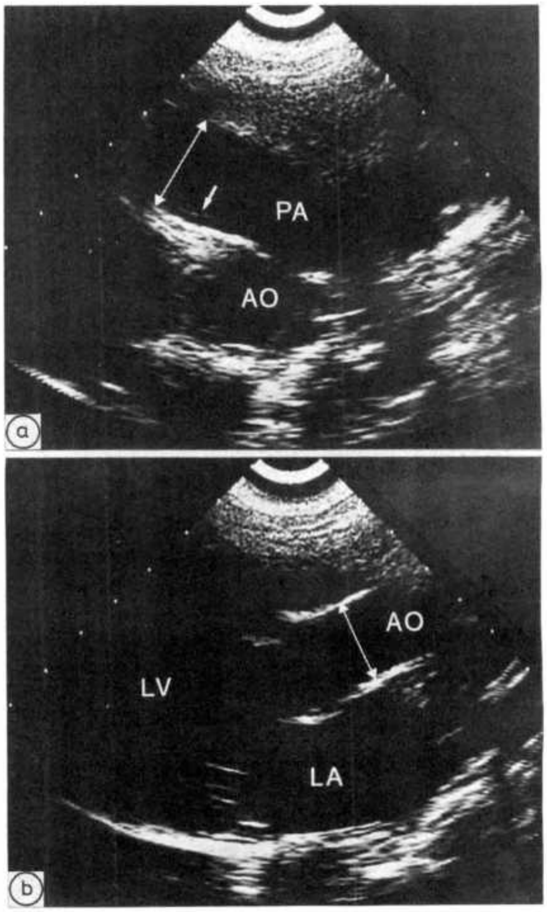

Fig 1 *Echocardiographic views used for measuring the diameters of the great arteries. (a) The pulmonary trunk was visualised in the parasternal long axis view of the right ventricular outflow tract. Measurements were made at the pulmonary valve level in end systole. One of the opened pulmonary valve leaflets is visible (arrow head). (b) The aortic root was visualised in the parasternal left ventricular long axis view. Its diameter was measured distal to the sinuses of Valsalva, where the aorta assumes a more cylindrical shape. A minimum gain was used to obtain clear and thin echo lines. AO, aortic root; PA, pulmonary trunk; LA, left atrium; LV, left ventricle.*

Table 1 *Regression equations relating echocardiographic diameters of the great arteries to body surface area in 153 infants and children (group 2)*

View	*Variable*	*Regression equation*	*r*	*RSS*	*SEE*
LAX	PA	0·031 + 2·258 (BSA)½	0·96	3·38	0·05
	Ao	0·084 + 1·944 (BSA)½	0·96	2·76	0·04
	PA:Ao	1·062 + 0·025 (BSA)	0·07	1·02	0·02
SAX	PA	0·108 + 1·969 (BSA)½	0·96	2·97	0·04
	Ao	0·153 + 1·958 (BSA)½	0·95	3·31	0·05
	PA·Ao	0·967 + 0·013 (BSA)	0·04	0·88	0·02

PA, pulmonary artery trunk; Ao, aortic root; LAX, parasternal long axis; SAX, parasternal short axis; r, correlation coefficient; RSS, residual sum of squares; BSA, body surface area; SEE, standard error of the estimate. All measurements were made in end systole by the leading edge method.

The 95% confidence interval was determined according to the following equation[10 11]:

$$y_c \pm [2F(0{\cdot}95,2,N-2)]^{1/2}\, s(y)\left[1 + 1/N + \frac{\sum(x_p - \bar{x})^2}{\sum(x_i - \bar{x})^2}\right]^{1/2}$$

In this equation the variables are y_c = calculated values corresponding to each x_p; $\bar{x}$ = mean value; x_i = x coordinates; N = number of points; F value: first number = level of confidence desired, second = the number of variables estimated, third = the number of degrees of freedom for error; s(y) = square root of the residual mean squares.

Results

All echocardiographic measurements were expressed as four functions of body surface area. In infants and children (group 2) the great vessel diameters were best fitted to the square root function of body surface area. Figure 2 shows the mean values and 95% prediction intervals. Table 1 lists the regression functions for these measurements and body surface area. The correlation coefficients were very high ($r \geqslant 0{\cdot}95$) and they were similar for measurements in the long axis and short axis parasternal views.

The pulmonary trunk to aortic root ratios, determined in the long axis and short axis views, were independent of body surface area (table 1) and the regression equation demonstrated a nearly straight horizontal line (fig 2c).

Neonates (group 1) differed from the main study population (group 2) in several respects (table 2). The pulmonary trunk was relatively large in the first 12 hours of life. Slightly but significantly smaller diameters were found in the groups that were 12–24 hours, 3–6 days, and 1–3 weeks old. In the 3–6 month age group the dimension of the pulmonary trunk was again equal to that at birth and from three months onwards there was a steady increase in pulmonary trunk size, related to age and body surface area (fig 3). In contrast, the aortic root dimension increased gradually with age from birth onwards. This difference in growth pattern was also expressed by the pulmonary trunk to aortic root ratio. In group 1A (age ⩽12 hours) the pulmonary trunk to aortic root ratio was 1·29 (0·12). This value was significantly larger ($p < 0{\cdot}005$) than in neonates aged 12–24 hours, in whom the ratio of the pulmonary trunk to the aortic root was 1·12 (0·10). In neonates aged 1–3 weeks the pulmonary trunk to aortic root ratio was 1·08 (0·05), which was not significantly different from the mean value in older

Table 2 *Echocardiographic measurements (mean (SD)) of the diameter (cm) of the great arteries in neonates, infants, and children*

				Clinical data					
Age	⩽12 h	12–24 h	3–6 day	1–4 wk	1–3 mnth	3–6 mnth	6–12 mnth	1 wk–15 yr	4 h–15 yr
No	10	10	15*	8	21	17	12	153	173
Weight (kg)	3·40 (0·27)	3·42 (0·33)	3·40 (0·29)	3·32 (0·40)	4·92 (0·66)	5·62 (1·08)	7·67 (0·79)		
BSA (m²)	0·21 (0·01)	0·21 (0·01)	0·21 (0·01)	0·21 (0·01)	0·26 (0·02)	0·29 (0·04)	0·37 (0·03)		
				Parasternal long axis					
PA	1·15 (0·09)	1·02 (0·05)	1·01 (0·09)	1·05 (0·05)	1·09 (0·11)	1·19 (0·11)	1·41 (0·14)		
Ao	0·89 (0·09)	0·92 (0·09)	0·93 (0·07)	0·98 (0·07)	1·04 (0·12)	1·12 (0·13)	1·34 (0·13)		
PA:Ao	1·29 (0·12)	1·12 (0·10)	1·09 (0·08)	1·08 (0·05)	1·06 (0·09)	1·07 (0·08)	1·05 (0·06)	1·05 (0·06)	1·09 (0·09)
				Parasternal short axis					
PA	1·05 (0·08)	0·98 (0·07)	0·96 (0·07)	1·03 (0·08)	1·08 (0·10)	1·15 (0·12)	1·33 (0·11)		
Ao	0·94 (0·12)	0·96 (0·07)	0·98 (0·10)	0·99 (0·08)	1·12 (0·11)	1·2 (0·1)	1·39 (0·13)		
PA:Ao	1·13 (0·13)	1·02 (0·10)	0·99 (0·11)	1·04 (0·10)	0·97 (0·09)	0·96 (0·09)	0·96 (0·06)	0·96 (0·06)	0·99 (0·09)

*These 15 subjects belong to the group of 20 neonates who were examined within 24 hours after birth. They were restudied 3–6 days after the initial examination.
See footnote to table 1 for abbreviations.

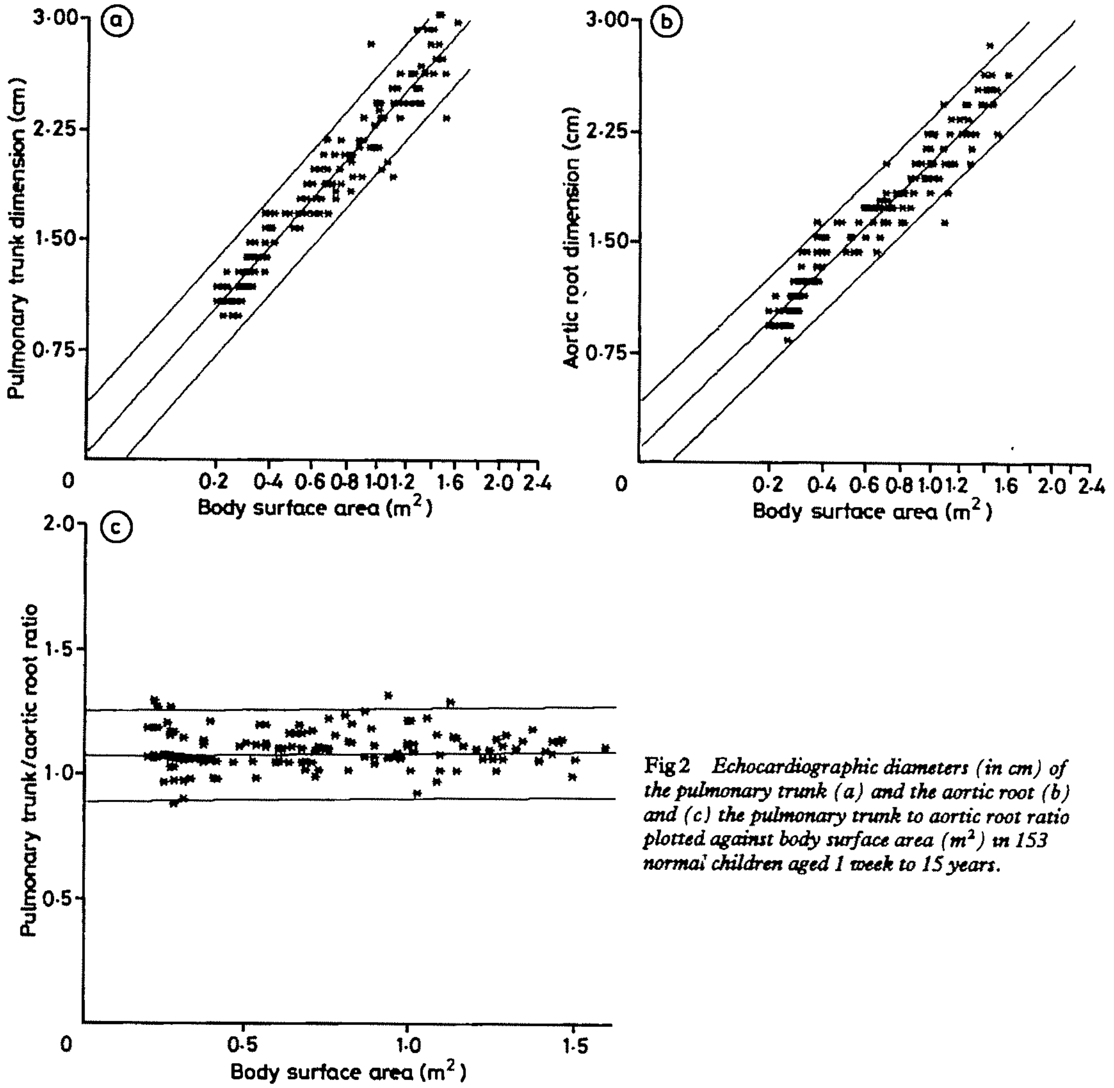

Fig 2 *Echocardiographic diameters (in cm) of the pulmonary trunk (a) and the aortic root (b) and (c) the pulmonary trunk to aortic root ratio plotted against body surface area (m²) in 153 normal children aged 1 week to 15 years.*

infants and in group 2 as a whole (1·05 (0·06)).

Eight of the 10 neonates in whom the echocardiographic diameters were obtained in the first 12 hours were restudied during the first week of life. The pulmonary trunk to aortic root ratio decreased considerably within one week after birth in all eight cases (fig 4).

Table 3 shows the differences between measurements of the great arteries obtained by different methods: in systole versus diastole, from the parasternal short axis view versus the long axis view, and the internal diameter of the pulmonary trunk versus the diameter obtained by the leading edge method. The diameter of the pulmonary trunk and aortic root was slightly larger in systole than in diastole ($p < 0·001$). The mean value of the pulmonary trunk increased by 4·3%, the mean value of the aortic root by 3·4%, while the pulmonary trunk:aortic root ratio remained unchanged. The pulmonary trunk in the parasternal short axis view was slightly smaller than in the long axis view ($p < 0·001$), whereas the aortic root in the parasternal short axis view was larger than in the long axis view ($p < 0·001$). Consequently, the pulmonary trunk to aortic root ratio in the parasternal short axis view (0·99) was smaller ($p < 0·001$) than in the long axis view (1·09). The

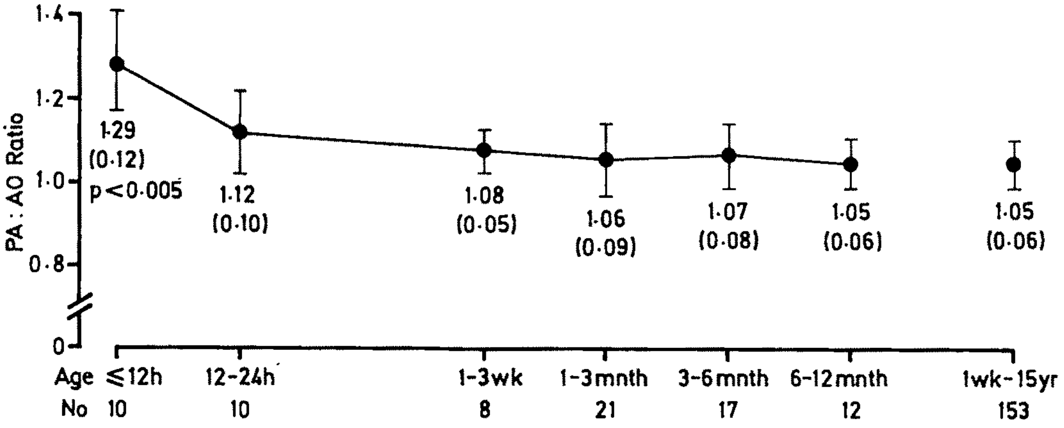

Fig 3 *Pulmonary trunk to aortic root ratio (mean (SD)) in different age groups during the first year of life compared with the mean value for all 153 subjects in group 2 (aged one week to 15 years).*

internal pulmonary trunk diameter (mean 1·55 cm) and the pulmonary trunk to aortic root ratio (1·05) derived from measurements of the internal diameter of the pulmonary trunk were slightly but significantly ($p < 0{\cdot}001$) smaller than those obtained by the leading edge method (mean 1·62 cm for pulmonary trunk diameter and 1·09 for pulmonary trunk to aortic root ratio).

Discussion

In contrast with the large number of M mode echocardiographic studies on aortic root dimension in normal children[12–16] there are only a few reports of pulmonary trunk size.[15,17] Simultaneous visualisation of both pulmonary arterial walls on M mode echocardiograms was difficult and measurements of the vessel diameter were unreliable[13] or gave widely scattered values.[15] Cross sectional echocardiographic data on pulmonary trunk size are equally scant. Sahn *et al* obtained normal values for cardiac and great vessel dimensions in the fetus and immediately after birth.[18] Aortic root and pulmonary trunk dimensions were reported by Snider *et al* in 110 normal subjects from the neonatal period to adulthood.[6] The usefulness of their data is limited by the choice of the echocardiographic sections: for simultaneous visualisation of both great arteries the investigators selected the parasternal short axis view which, according to their own experience, causes considerable underestimation of the pulmonary artery size. This was confirmed in our study. We found it more difficult and time consuming to obtain a satisfactory image of the wall of the pulmonary trunk in the parasternal short axis view than in the parasternal long axis view and we also tended to underestimate the pulmonary trunk size in the short axis view, although the difference was less pronounced than that observed by Snider *et al.*[6]

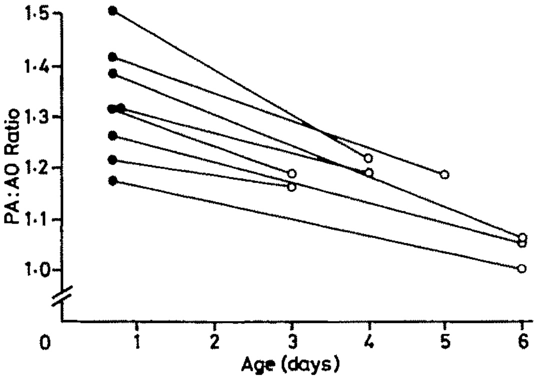

Fig 4 *Sequential measurements of pulmonary trunk to aortic root ratio in eight neonates during the first week of life.*

Our results indicate that, with the exception of the first weeks of life, the dimensions of both great arteries show a linear correlation with the square root of the body surface area. This function also gave the best fit in an earlier cross sectional echocardiographic study.[6] In M mode studies the size of the aortic root varied linearly with body surface area[13,15,16] or in relation to the cubic root of the body surface area.[14] The graphic representation (fig 2) of the dimensions of great artery over a large range of body surface area should be useful in identifying abnormalities, particularly defects causing a left to right shunt,[3,7] tetralogy of Fallot,[8] or coarctation of the aorta.[19]

The pulmonary trunk to aortic root ratio was remarkably constant (mean 1·05 (0·06)) in infants

Table 3 *Influence of method of measurement on dimensions of great arteries in infants and children (n = 173)*

Variable	*Dimension*	*Mean value of measurement (cm)*		*Difference of the means*	*p value*
		Diastole versus systole			
Phase of cardiac cycle	PA LAX)	1·62	1·69	0·07	<0·001
	Ao (LAX)	1·49	1·54	0·05	<0·001
	PA: Ao (LAX)	1·09	1·10	0·01	NS
		Short axis versus long axis			
Echocardiographic plane	PA	1·54	1·62	0·08	<0·001
	Ao	1·56	1·49	0·07	<0·001
	PA:Ao	0·99	1·09	0·10	<0·001
		Internal diameter versus leading edge			
Measuring technique	PA (LAX)	1·55	1·62	0·06	<0·001

See footnote to table 1 for abbreviations.

aged more than one month and throughout childhood; this gave a nearly straight horizontal regression line and a narrow confidence interval for the relation between pulmonary trunk to aortic root ratio and body surface area (fig 2). The finding that the pulmonary trunk is slightly larger than the aortic root confirms the results of previous studies on smaller numbers of normal children, in which the same echocardiographic view (parasternal long axis) and measuring sites were selected.[5 7] Our results do not accord with those of Snider *et al* who found a wide scatter of pulmonary trunk to aortic root ratios and a pulmonary trunk dimension smaller than the aortic root dimension in most children.[6] This difference may be partly explained by their use of the parasternal short axis view which, as shown in our study, leads to underestimation of the pulmonary trunk dimension and overestimation of the aortic root dimension.

We did not attempt to validate our results against invasive techniques or postmortem measurements. Our data, however, generally accord with such studies. Sievers *et al* reported on the angiocardiographic dimensions of the great arteries in 24 normal children.[4] The mean values of pulmonary trunk dimension (at the pulmonary valve level) and aortic root dimension (just distal to the sinuses of Valsalva) give a pulmonary trunk to aortic root ratio of 1·06 in systole and 1·07 in diastole. In a pathological study De la Cruz *et al* reported that the ratio of the square of the orifice of the pulmonary artery to the aortic root was 1·16,[1] which is slightly larger than the ratio of the great vessel diameters that we obtained. The considerable change in the dimensions of the great arteries that we found in the first days of life have not been reported before. Sahn *et al* reported normal data on great vessel diameters[18] but this study was limited to the cardiac anatomy of the fetus in the second half of pregnancy and the neonate in the first 36 hours after birth. In their study, which included neonates, Snider *et al* related great vessel diameters solely to body surface area and not to age,[6] which makes it impossible to detect very early age-related changes. As expected the pulmonary trunk diameter was found to be relatively large at birth. Surprisingly, however, this dimension decreased rapidly. The largest diameters were noted in neonates who were <12 hours old. Significantly smaller diameters were found in those aged 12–24 hours and 3 days–3 weeks. In the 3–6 month age group the mean pulmonary trunk diameter was again equal to the measurement at birth and from three months on there was a steady increase in pulmonary trunk size that was related to body surface area and age. By contrast, the aortic root dimension increased gradually from birth onwards. Consequently the pulmonary trunk to aortic root ratio was greatest during the first hours of life but by one week had decreased rapidly to reach the "normal" value obtained in older infants and children. This change was distinctly shown in a subgroup of eight neonates in whom echocardiographic examinations were performed within 12 hours after birth and repeated in the course of the first week of life. Obviously, postnatal physiological changes of the circulation profoundly affect the size of the great arteries. The rapid decrease in the size of the pulmonary trunk coincides with the dramatic decrease in pulmonary vascular resistance and pressure and the redistribution of blood flow after birth, as extensively shown in fetal lambs.[20].

The dimensions of the great arteries varied depending on the measuring technique. We systematically used the leading edge method which has been shown to be the most accurate.[21] In some children, however, this method was found to be unreliable when used to measure the pulmonary trunk diameter from the parasternal short axis view. In this view the anterior edge of the pulmonary artery tends to be blurred. In these subjects only the inner diameter could be assessed. In an attempt to evaluate the effect of the measuring technique on vessel diameter we used both methods (leading edge to leading edge and inner to inner surface) to measure the pulmonary trunk in the parasternal long axis view. The internal diameter measurement gave slightly smaller values than the leading edge method. The fact that the difference was very small (mean 0·06 cm) and negligible for clinical purposes may be because of our echocardiographic technique. We used a high resolution system and a minimum gain to obtain clear and thin echo lines and this somewhat reduced the wall thickness of the vessel.

When it is imaged in the parasternal plane, and particularly from the short axis view, the pulmonary trunk appears to change size with the cardiac cycle. We therefore measured the diameters of the great arteries in systole and diastole. Previous studies have shown that the cross sectional area of the aorta increases 5%–10% during systole while that of the pulmonary artery increases 2% to 18%.[22 23] Similar changes in diameter were seen in our study when the great artery dimensions were measured in the parasternal long axis view. The mean end systolic aortic root diameter was 3·4% larger than the end diastolic diameter, while the pulmonary trunk diameter increased by 4·3%. As these changes occurred simultaneously the pulmonary trunk to aortic root ratio was not influenced by the cardiac cycle. In the parasternal short axis view no consistent pattern in the systolic-diastolic changes was found. In most patients the diameter of the pulmonary trunk increased in systole, but in some it decreased. This decrease has also been reported by others when they measured the pulmonary trunk in the parasternal short axis view and has been attributed to a systolic movement of the pulmonary artery in such a way that the examining plane no longer passes through the centre of the vessel.[24] Our results indicate that this factor has no major influence in the parasternal long axis view in which we found a small but consistent systolic increase in the size of the pulmonary trunk.

Our study provides normal values for cross sectional echocardiographic measurements of the pulmonary trunk and aortic root in neonates, infants, and children. We found that the parasternal long axis view was more reliable than the short axis view for measuring the pulmonary trunk. In contrast with the fairly wide 95% confidence intervals for pulmonary trunk and aortic root size, the pulmonary trunk to aortic root ratio showed little individual variability and was remarkably constant throughout infancy and childhood. The graphs relating these measurements to age (in neonates) or body surface area (in children older than one week) should be useful in assessing patients with congenital heart disease, particularly those with a decrease or increase in pulmonary blood flow.

References

1 De La Cruz MW, Anselmi G, Romero A, Monroy G. A qualitative and quantitative study of the ventricles and great arteries of normal children. *Am Heart J* 1960;**60**:675–90.

2 van Meurs-van Woezik H, Klein HW, Krediet P. Normal internal calibres of ostia of great arteries and of aortic isthmus in infants and children. *Br Heart J* 1977;**39**:860–5.

3 Jarmakani JM, Graham TP, Benson DW, Canent RV, Greenfield JC. In vivo pressure-radius relationships of the pulmonary artery in children with congenital heart disease. *Circulation* 1971;**43**:585–92.

4 Sievers HH, Onnasch DG, Lange PE, Bernhard A, Heintzen P. Dimensions of the great arteries, semilunar valve roots and right ventricular outflow tract during growth. Normative angiocardiographic data. *Pediatr Cardiol* 1983;**4**:189–96.

5 Gussenhoven WJ, van Leenen BF, Kuis W, de Villeneuve VH, Bom N, van Meurs-van Woezik H. Comparison of internal diameter of great arteries in congenital heart disease. A cross-sectional echocardiographic study. *Br Heart J* 1983;**49**:45–50.

6 Snider AR, Enderlein MA, Teitel DF, Juster RP. Two-dimensional echocardiographic determination of aortic and pulmonary artery sizes from infancy to adulthood in normal subjects. *Am J Cardiol* 1984;**53**:218–24.

7 Denef B, Dumoulin M, Van der Hauwaert LG. Usefulness of echocardiographic assessment of right ventricular and pulmonary trunk size for estimating magnitude of left-to-right shunt in children with atrial septal defect. *Am J Cardiol* 1985;**55**:1571–5

8 Lappen RS, Riggs TW, Lapin GD, Paul MH, Muster AJ. Two-dimensional echocardiographic measurement of right pulmonary artery diameter in infants and children. *J Am Coll Cardiol* 1983;**2**:120–6.

9 Boothby W, Sandiford RB. Normographic charts for the calculation of the metabolic rate by the gasometer method. *Boston Med Surg J* 1921;**185**:337.

10 Aubert AE. LILLY. A linear least squares curves fitting program. *Handshake* 1985;**9**:25–32.

11 Daniel C, Wood FS. *Fitting equations to date.* New York: J Wiley and Sons, 1980:10–3.

12 Lundstrom NR. Clinical applications of echocardiography in infants and children. *Acta Paediatr Scand* 1974;suppl 243:5–38.

13 Epstein M, Goldberg SJ, Allen HD, Konecke L, Wood J. Great vessel, cardiac chamber and wall growth patterns in normal children. *Circulation* 1975;**51**: 1124–9.

14 Henry WL, Ware J, Gardin JM, Hepner SI, McKay J, Weiner M. Echocardiographic measurements in normal subjects. Growth-related changes that occur between infancy and early adulthood. *Circulation* 1978;**57**:278–85.

15 Rogé CL, Silverman NH, Hart PA, Ray RM. Cardiac structure growth pattern determined by echocardiography. *Circulation* 1978;**57**:285–90.

16 Oberhänsli I, Brandon G, Friedli B. Echocardiographic growth patterns of intracardiac dimen-

sions and determination of function indices during the first year of life. *Helv Paediatr Acta* 1981;**36**: 325–40.

17 Hagan AD, Deely WJ, Sahn D, Friedman WF. Echocardiographic criteria for normal newborn infants. *Circulation* 1973;**48**:1221–6.

18 Sahn DJ, Lange LW, Allen HD, *et al.* Quantitative real-time cross sectional echocardiography in the developing normal human fetus and newborns. *Circulation* 1980;**62**:588–97.

19 Morrow WR, Huhta JC, Murphy DJ, McNamara DG. Quantitative morphology of the aortic arch in neonatal coarctation. *J Am Coll Cardiol* 1986;**8**:616–20.

20 Rudolph AM. *Congenital diseases of the heart.* Chicago: Yearbook Medical Publishers, 1974: 17–48.

21 Feigenbaum HF. *Echocardiography.* 3rd ed. Philadelphia: Lea and Febiger, 1981:110–4.

22 Greenfield JC, Patel DJ. Relation between pressure and diameter in the ascending aorta of man. *Circ Res* 1962;**10**:778–81.

23 Greenfield JC, Griggs DM. Relation between pressure and diameter in main pulmonary artery in man. *J Apply Physiol* 1963;**18**:557–9.

24 Goldberg SJ, Allen HD, Marx GR, Flinn CJ. *Doppler echocardiography.* Philadelphia: Lea and Febiger, 1985:80–6.

Br Heart J 1987;58:635–43

Pathological changes induced by repeated percutaneous transluminal coronary angioplasty

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SUMMARY The histopathological appearances of seven coronary arteries obtained from four patients after repeated percutaneous transluminal coronary angioplasty were analysed. A complex picture was found; typically there were ruptured atherosclerotic plaques, plaque dissection, and a fibrous tissue response. The histopathological appearance of older and more recent fibrous lesions was different. Older lesions contained more collagen and elastin fibres, whereas recent ones had more loosely arranged connective tissue containing abundant glycosaminoglycan and readily identifiable cells. The fibrous tissues tended to be damaged at the sites of previous injury and where the vessel wall was thinnest. In five of the seven arteries there was evidence of a repeated fibrous response to injury with partial or total rupture of the original media. In one instance a repair response within a pre-existing atherosclerotic plaque had caused restenosis.

The results indicate that restenosis after repeated percutaneous transluminal coronary angioplasty, like restenosis after a first procedure, is mainly the result of fibrocellular tissue response to injury of the wall tissues. Because older (that is more mature) repair tissue contains fewer cells and more connective elements than younger repair tissue (that is the loosely arranged connective tissue found soon after angioplasty), when it is disrupted by a further angioplasty procedure it is less capable of producing tissue that will obstruct the lumen. This may explain why in the majority of patients with restenosis repeated percutaneous transluminal coronary angioplasty is successful. The present study also showed that occasionally plaque haemorrhages may become organised and incorporated into the pre-existing atherosclerotic lesion.

Restenosis is a major complication of percutaneous transluminal coronary angioplasty. Follow up angiography showed a high frequency (33·6%) of restenosis in patients on a register of percutaneous transluminal coronary angioplasty procedures.[1] Treatment of coronary restenosis by repeat percutaneous coronary angioplasty has a high immediate success rate and a low complication rate, but follow up angiographic examinations showed restenosis in 34% of these patients.[2]

Pathological changes underlying restenosis after a first coronary angioplasty procedure have been recognised.[3–14] Although several questions still remain the consensus is that in most instances restenosis is caused by fibrocellular proliferation which is probably prompted by injury to the vascular smooth muscle cells. There are two reports of restenosis caused by atherosclerotic plaques in the absence of morphological lesions that were attributable to the angioplasty procedure.[8 10]

To the best of our knowledge the pathological changes found after repeated percutaneous transluminal coronary angioplasy have not been described before.

Patients and methods

The heart specimens were obtained from four patients. Table 1 gives the relevant clinical data. Repeated percutaneous transluminal coronary angioplasty of seven arteries had been performed because of recurrent angina pectoris and associated

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Table 1 *Clinical data associated with pathological findings*

Case	*Age (yr)*	*Sex*	*Clinical diagnosis*	*PTCA*	*Site of PTCA*	*No of PTCAs*	*Atherosclerosis of other coronary arteries*	*Cause of death*
1	63	M	AP, SMI, AMI	Elective and emergency	RCA (1) LAD (6) LCx (11) Diag (9)	3 5 2 4	Moderate in distal part of RCA, LAD, and LCx	AMI
2	68	M	AP, SMI	Elective	LAD (6, 7)	2	Severe in RCA and LCx	AMI
3	54	M	AP, chronic renal failure	Elective	LAD (7)	2	Moderate in RCA and LCx	AMI
4	72	M	AP, AMI	Elective and emergency	LAD (6, 7) LCx (11) OM (12)	1 2 1	Moderate in RCA	AMI

The numerals in parentheses indicate the arterial segment according to the American Heart Association Committee Report.[22] Moderate atherosclerotic lesions, 50–75% stenosis, severe atherosclerotic lesions >75% stenosis. AMI, acute myocardial infarction, AP, angina pectoris; diag, diagonal; LAD, left anterior descending coronary artery; LCA, main left coronary artery; LCx, left circumflex artery; OM, obtuse marginal artery; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; SMI, scarred myocardial infarct.

restenosis. Patients had had from one to five percutaneous transluminal coronary angioplasty procedures. Table 2 shows the interval between the last percutaneous transluminal coronary angioplasty procedure and death.

Pathological examination

In each case the complete heart was available for study. After fixation in buffered formalin, the coronary arteries were removed from the epicardial surface and decalcified before sectioning. The arteries in which the percutaneous transluminal coronary angioplasty had been performed were sectioned serially every 1–2 mm for 8 cm from the origin of the vessels. The other coronary arteries were sectioned serially every 3 mm for 6 cm from the origin. All blocks were routinely processed and 5 μm thick sections were prepared. The sections were stained with haematoxylin and eosin, an elastic stain counter-

Table 2 *Pathological findings in coronary arteries after repeated percutaneous transluminal coronary angioplasty*

Case	*Artery**		*No of PTCAs*	*Interval between PTCA and death*	*Wall laceration*
					Intima
1	RCA	(1)	3	2 hours 1-month 23 days 5 months, 7 days	Plaque rupture, recent haemorrhage older plaque dissection, organised haemorrhage within plaque
	Diag	(9)	4	2 hours 2 months, 15 days 5 months, 22 days 7 months	Plaque rupture, recent haemorrhage, recent and earlier laceration of fibrocellular tissue; gap filled with young proliferative tissue
	LAD	(6)	5	2 hours 2 months, 15 days 3 months. 6 days 5 months, 22 days 7 months, 10 days	Plaque rupture, recent haemorrhage; old plaque rupture, organised haemorrhage; dissection and laceration of fibrocellular tissue (dating from an earlier procedure) extending into main LCA
	LCx	(11)	2	2 months, 15 days 7 months, 10 days	Plaque rupture, organised haemorrhage, laceration of fibrocellular tissue (dating from an earlier procedure); dissection and gap filled with young, proliferative fibrous tissue
2	LAD	(6, 7)	2	3 months, 10 days 4 months, 7 days	Plaque rupture, dissection; fibrous response and organised haemorrhage (continued into main LCA)
3	LAD	(7)	2	2 months, 18 days 6 months, 17 days	Dissection and rupture plaque-free wall into media; old plaque dissection and rupture organised haemorrhage; fibrocellular tissue (dating from an earlier procedure) in old dissection; young fibrous tissue in more recent laceration
4	LCx	(11)	2	1 day 10 months, 13 days	Plaque dissection and rupture into media organised haemorrhage, dissection partially filled with thrombus and partially with fibrous tissue

*Segment(s) of the coronary arteries that were dilated are shown in parentheses (according to the American Heart Association Committee Report).[2]

stained with Van Gieson's stain, and a phosphotungstic acid haematoxylin stain. The blocks taken from the sites of the percutaneous transluminal coronary angioplasty were serially sectioned, whereas step sections were taken from the remaining blocks. When necessary additional sections were also mounted.

The myocardium was studied by cutting the heart in parallel slices, perpendicular to the left ventricular long axis. Full thickness slices were then taken for histological examination, at different levels, to include both the left and right ventricles.

Results

Table 2 shows the most important pathological features found in the coronary arteries.

Dissection and rupture of pre-existing atherosclerotic plaques was detected in all seven arteries. There was plaque rupture with recent haemorrhage and mural thrombosis in three arteries (case 1: right coronary artery, diagonal branch, left anterior descending coronary artery), which had been dilated two hours before death.

Pre-existing eccentric atherosclerotic plaques were damaged where the plaque was attached to the underlying media and pre-existing concentric lesions were damaged at their thinnest part (fig 1). Rupture sites and dissection clefts were filled with fibrous tissue, which indicated the stage of healing. Laceration of repair tissue was clearly indentifiable. Older repair tissue contained more collagen and elastin fibres than more recently formed tissue which had a looser texture and contained abundant glycosaminoglycans and readily identifiable cells. Disruption of fibrous tissue tended to occur at the site of earlier injury, generally where the vessel wall was thinnest. In five of seven arteries evidence of a repeated fibrous response to injury was accompanied by partial or total rupture of the original media (fig 2). In one instance (case 1: left anterior descending coronary artery) cholesterol filled the dissection cleft between a pre-existing atherosclerotic plaque and the media (fig 3).

In three arteries attenuation and separation of smooth muscle cells had disrupted the media at the site that initially was considered to be plaque free (fig 4).

In one instance (case 4) there was massive dissection of the coronary arteries. The first attempt to dilate the left circumflex artery (10 months and 13 days before death) probably caused plaque dis-

Media	*Medial smooth muscle cells attenuation/disruption*	*Thrombosis*	*Restenosis*	*Tissue response underlying restenosis*	
				Fibrocellular proliferation	*Atherosclerosis*
	Attenuation	Recent thrombus	+	+	–
Partial and total rupture	(Rupture)	Recent thrombus	+	–	+
Partial and total rupture	Attenuation/disruption	Recent thrombus	+	+	–
	(Rupture)	–	+	+	+
Laceration of plaque-free wall	Attenuation, disruption of plaque-free wall	–	+	+	–
Partial and total rupture	(Rupture)	–	+	+	–
Partial and total rupture, dissection	(Rupture)	–	+	+	–

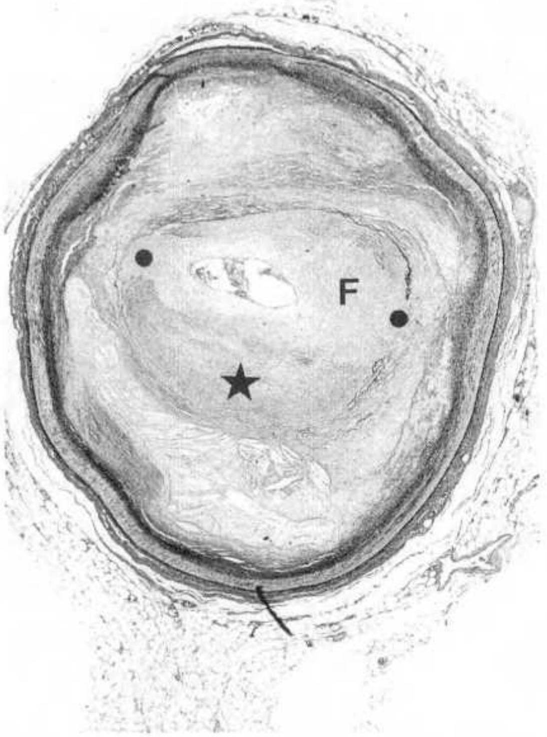

Fig 1 *Photomicrograph showing concentric atherosclerotic obstruction of a coronary artery with tears where the thickness of the plaque and of the fibrocellular tissue layer was thinnest (black dots) after previous percutaneous transluminal coronary angioplasty (asterisk). A new layer of fibrocellular tissue (F) has led to restenosis. Elastic tissue stains (original magnification, × 17·5).*

section and rupture and limited dissection of the media. Fibrous tissue covered part of the false lumen. A subsequent attempt to dilate the left circumflex artery (a day before death) caused further dissection. During the second attempt at the same session the catheter was guided into the false lumen and further on into the obtuse marginal branch. Inflation of the balloon led to a dissection extending into the intramyocardial branches (fig 5). Instant cardiac shock developed and the patient died.

In all seven arteries there was narrowing (including pre-existing obstructive lesions not previously treated by balloon dilatation) of $\geqslant 50\%$ of the lumen; thus all met the clinical criteria for restenosis.[15] In six of the seven instances restenosis was caused by proliferation of fibrocellular tissue, after laceration of the vessel wall. In one instance (case 1: right coronary artery) there was restenosis caused by a repair process within a pre-existing atherosclerotic plaque (fig 6). The artery showed several surface irregularities that were covered by recent thrombosis; these were considered to be an effect of the most recent attempt at dilatation (two hours before death). Within pre-existing atherosclerotic plaques there were highly disorganised and cellular areas caused by proliferation of fibroblasts intermingled with many lipid laden macrophages and the occasional lymphocyte and dispersed iron deposits. In one artery (case 1: left anterior descending coronary artery) we found both a repair process within an atheroma and a fibrocellular tissue proliferation.

The myocardium of each of the four patients showed features of healed and acute myocardial infarction. In each of these instances death was considered to be related either directly to the last procedure or to pre-existing generalised obstructive coronary atherosclerosis (see table 1).

Discussion

We studied four hearts obtained from patients who died after repeated percutaneous transluminal coronary angioplasties for coronary artery restenosis in whom the initial procedure had been successful.

Histological examination of the seven arteries showed a complex structure, dominated by arterial wall laceration involving both pre-existing atherosclerotic plaques and fibrous repair tissue that was considered to have been produced in response to the initial injury. Indeed, in all instances the changes found at microscopy were in accord with the clinical history of repeated percutaneous transluminal coronary angioplasties. There was plaque rupture with dissection and damage to the underlying media in each instance. Laceration usually occurred at the end of the plaque in eccentric lesions and at the thinnest part of the arterial wall in concentric atherosclerotic lesions. There was fibrous tissue at the injury site characterised by well formed collagen and elastin fibres. Subsequent laceration of the arterial wall had caused further injury to the repair tissues and these newer sites were covered by a fibrocellular tissue rich in glycosaminoglycans that contained fewer collagen and elastin fibres. The history of each percutaneous transluminal coronary angioplasty procedure could be followed almost step by step.

In one artery cholesterol deposits were embedded within fibrous tissue at a site of initial plaque dissection with laceration of the media. This finding unequivocally demonstrates that atheromatous plaque rupture had occurred and that cholesterol embolisation is a potential complication of the procedure. Peripheral cholesterol embolisation in man

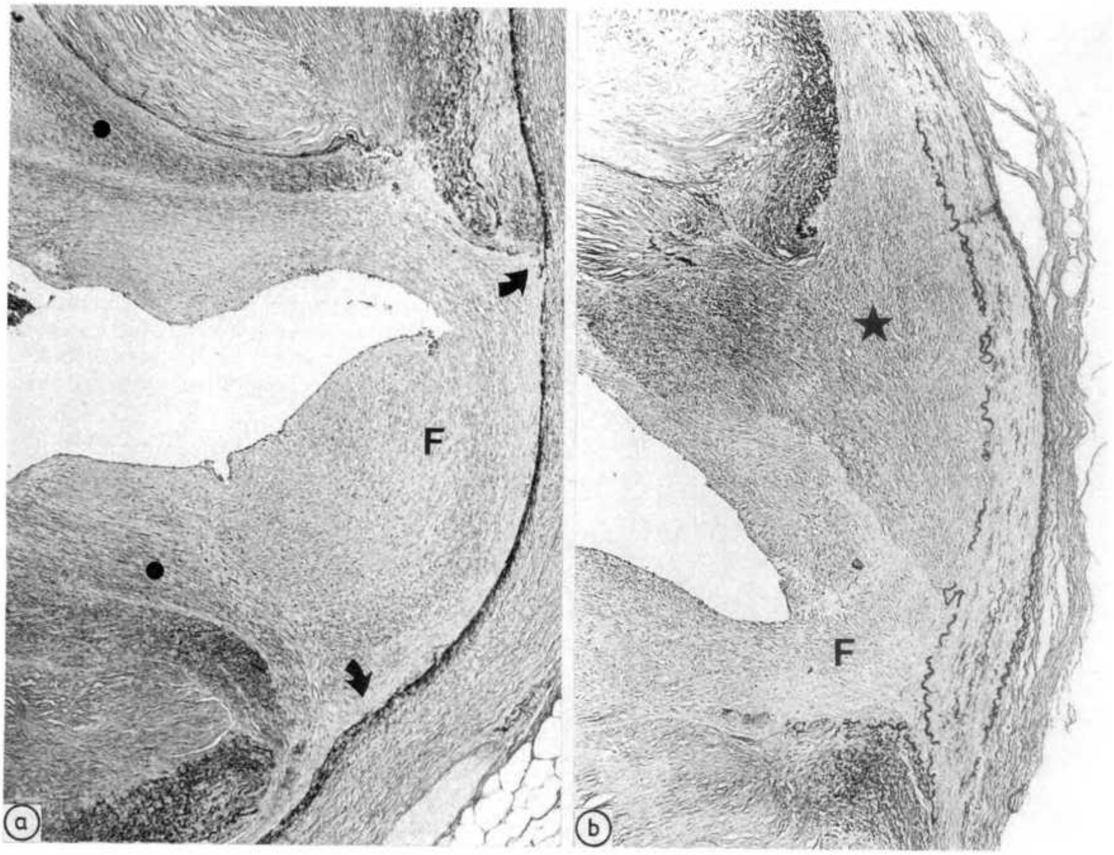

Fig 2 *Photomicrograph showing different stages of fibrocellular tissue response in coronary arteries after repeated percutaneous transluminal coronary angioplasties. (a) Site from which pre-existing media has disappeared (arrows). This is filled with relatively young fibrocellular tissue (F). This tissue covers a layer of fibrocellular tissue containing more elastin and collagen fibres, indicating a response to an earlier procedure (black dots). (b) An area of intimal disruption with superficial abrasion of the media. The gap is filled partly by fibrocellular tissue produced in response to an earlier procedure (asterisk) and partly by more loosely textured connective tissue, indicating a more recent origin (F). Elastic tissue stains a and b (original magnification,* × *55).*

has been reported,[14 16] but seems to be rare. A search for such emboli is tedious, however, and small emboli may be easily overlooked, as shown by experimental animal studies.[17 18]

Despite the histological complexity of the lesions, we identified attentuation of smooth muscle cells with separation and disruption of the media in three arteries. The remaining specimens showed partial medial rupture. The interpretation of changes in the smooth muscle cells of the media of coronary arteries is not easy. Advanced arterial atherosclerosis usually produces thinning of the media with attentuation of smooth muscle cells. But we also found changes that were highly suggestive of overstretching in segments of media without substantial intimal changes and when there was only a slightly elevated atheromatous lesion. This impression was supported by the observation of fragmented and often curly elastin fibres within the segments, which was commonly accompanied by an increase in fibrous tissue. These changes are distinct from the obvious thinning that occurs in association with atherosclerosis that was described by Isner and Fortin.[19]

It is tempting to view the observed changes in the media as being caused by overstretching of the wall by the radial pressure of the balloon. Attentuation and disruption of smooth muscle cells have also been

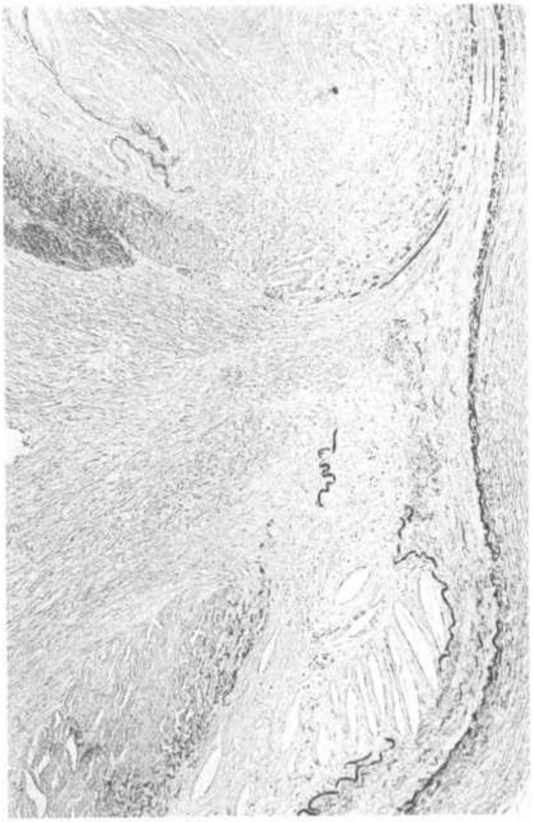

Fig 3 *Photomicrograph showing cholesterol clefts within a dissection, which were encapsulated by fibrocellular tissue in response to injury. Elastic tissue stain (original magnification,* × *55).*

reported by Düber *et al.*[13] They described necrosis of smooth muscle cells as a feature that occurs after vessel wall dilatation.

Dissection is another hazard of repeated percutaneous transluminal coronary angioplasty. This occurred in patient 4. The initial procedure had resulted in a dissection, which became partially filled with thrombus and partially coated by fibrous tissue. The repeat percutaneous transluminal coronary angioplasty procedure produced further dissection and the catheter was guided through the false channel from the left circumflex artery into the obtuse marginal branch. Inflation of the balloon then caused a massive dissection that extended into the myocardium and immediately caused death.

The results indicate that restenosis after repeated percutaneous transluminal coronary angioplasty is caused by a fibrocellular tissue response that resembles the major event causing restenosis after the first attempt.[3-14] This is not surprising as the fibrocellular tissue reaction depends upon the presence of viable cells activated by the procedure.[3] In patients who have repeated percutaneous transluminal coronary angioplasty and restenosis there is evidence of a potent growth factor and the aggregation of platelets at sites of laceration may be vital to this process.[20 21] In theory the more advanced the maturation of the fibrocellular response, that is when there is more collagen and fewer cells, the less likely is a second injury to cause further tissue response because the injury inflicted by the balloon affects only the acellular fibrous tissue. Because older (that is more mature) repair tissue contains fewer cells and more connective elements than

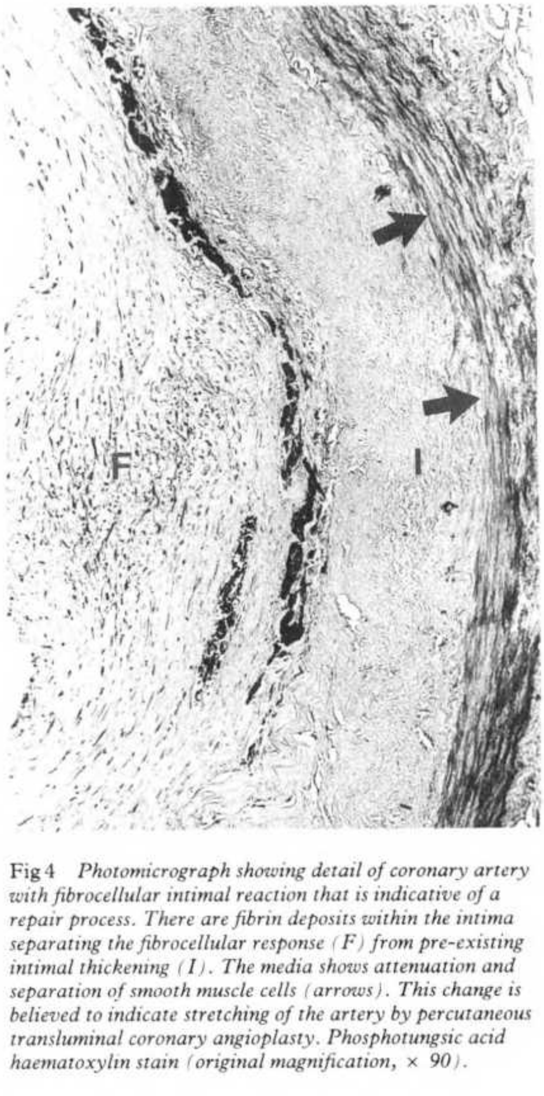

Fig 4 *Photomicrograph showing detail of coronary artery with fibrocellular intimal reaction that is indicative of a repair process. There are fibrin deposits within the intima separating the fibrocellular response (F) from pre-existing intimal thickening (I). The media shows attenuation and separation of smooth muscle cells (arrows). This change is believed to indicate stretching of the artery by percutaneous transluminal coronary angioplasty. Phosphotungsic acid haematoxylin stain (original magnification,* × *90).*

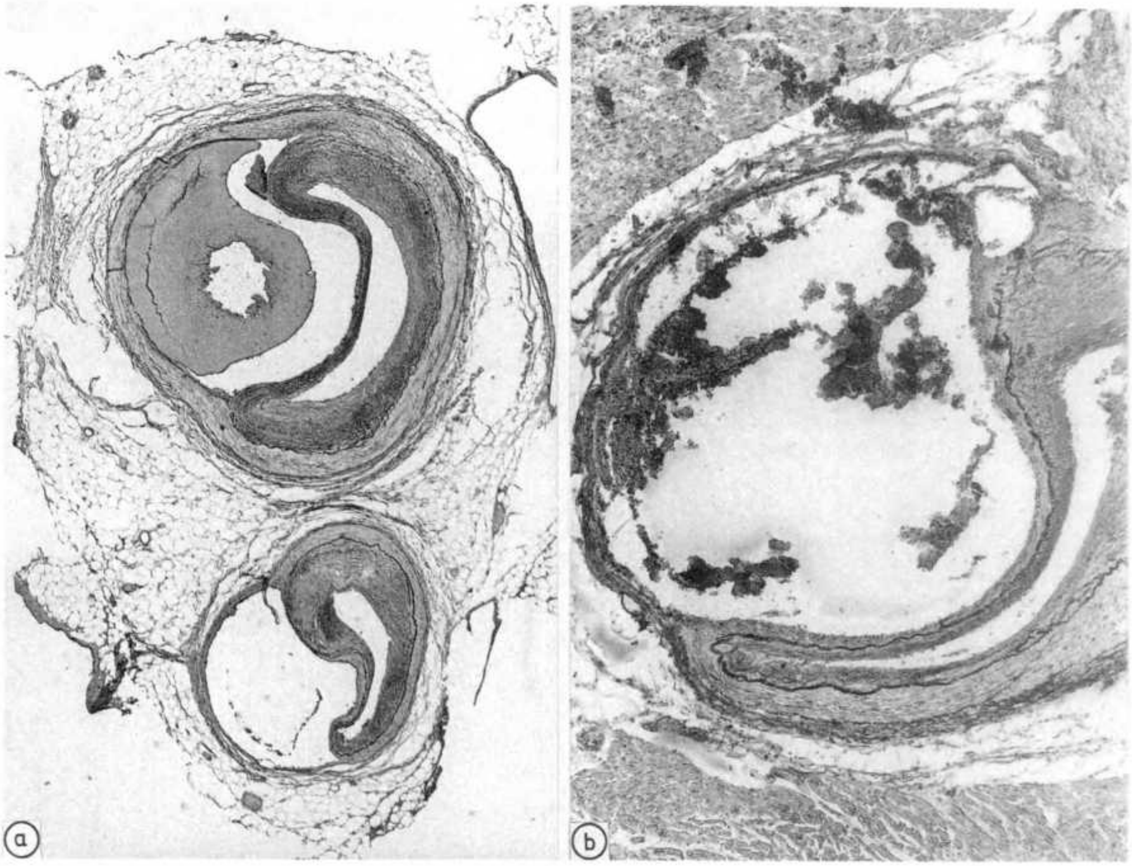

Fig 5 *Photomicrograph showing medial dissection extending from the epicardial artery into intramyocardial branches. (a) Cross section through the obtuse marginal artery and a side branch, both showing medial dissection. (b) Extension of the dissection into an intramyocardial branch. Elastic tissue stains (a) original magnification, × 21; (b) original magnification, × 55).*

younger repair tissue (that is the loosely arranged connective tissue found soon after angioplasty), when it is disrupted by a further angioplasty procedure it is less capable of producing tissue that will obstruct the lumen. This maturation of the initial tissue response may explain why a repeat percutaneous transluminal coronary angioplasty is successful in most patients with restenosis. The composition of the atherosclerotic plaque will determine whether or not the procedure will achieve lasting success. In plaques that are mainly composed of dense fibrous tissue and almost acellular, the tissue response leading to restenosis may be minimal or even absent. On the other hand, plaque injury to cellular tissues may lead to an early response and restenosis. These theoretical considerations fit nicely with the practical approach presently advocated in patients in whom a repeat angiogram reveals restenosis. Redilatation, under such circumstances, should primarily be based on the severity of the angina pectoris, rather than on the results of the various testing procedures.[15]

We also found that plaque haemorrhages, which are almost certainly the result of the dilatation procedure, may become organised and incorporated into the pre-existing atherosclerotic lesion. Occasionally this may be the sole reason for early restenosis in cases where this particular mechanism probably accelerates "normal" atherosclerosis. These observations could explain why Waller *et al* reported that three out of four cases of late restenosis were caused by "classic" atherosclerotic lesions

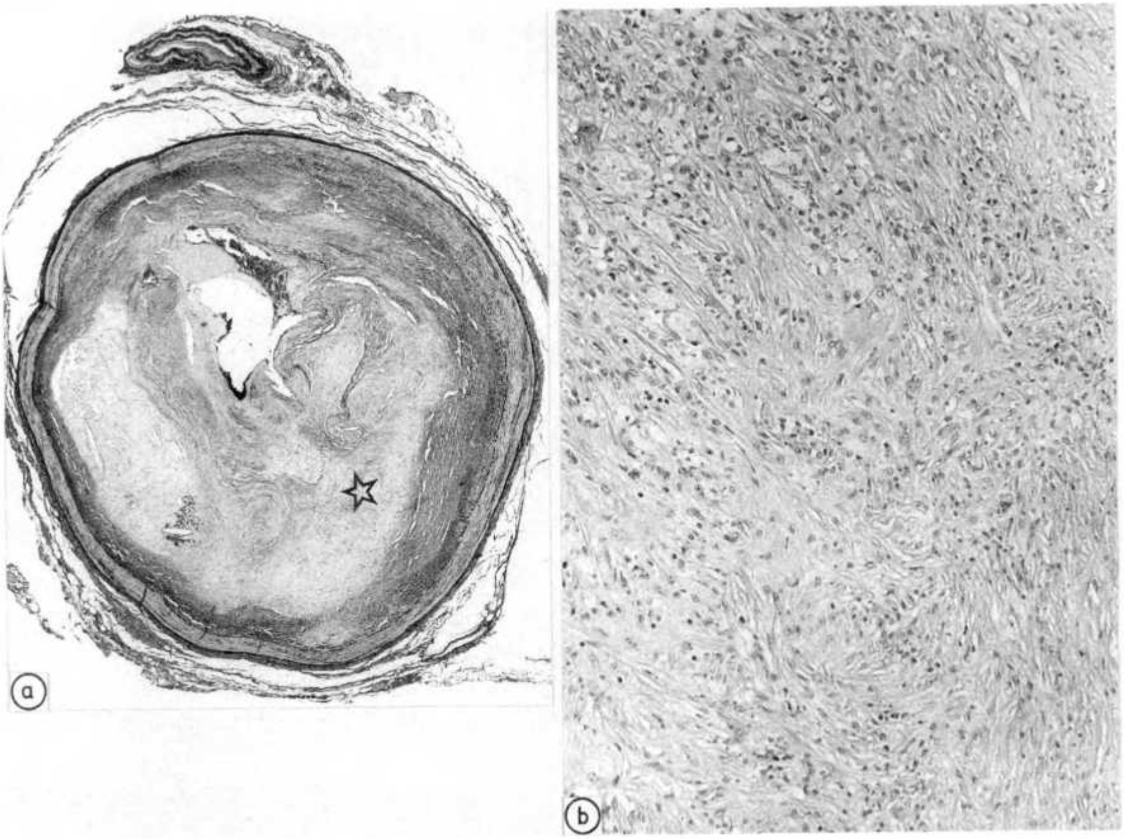

Fig 6 *Photomicrograph showing cross section through a coronary artery with severely obstructive atherosclerotic lesions after percutaneous transluminal coronary angioplasty. (a) Overall view showing several sites of laceration. The area indicated by the asterisk is shown in detail in (b). It shows a organising plaque haemorrhage. (a) Elastic tissue stain (original magnification × 14); (b) haematoxylin and eosin stain (original magnification × 90).*

without any signs attributable to a previous percutaneous transluminal coronary angioplasty.[8] Similarly, Giraldo *et al* described a successful percutaneous transluminal coronary angioplasty of the posterior descending coronary artery, while necropsy 69 day later showed a 75% luminal obstruction by a "common atherosclerotic plaque".[10]

The present study indicates that fibrocellular tissue proliferation is the most common mechanism underlying restenosis, and that healing of an injured atherosclerotic plaque may occasionally be an alternative mechanism.

During the course of this study Dr Ueda was on a leave of absence from the Department of Pathology, Osaka City University Medical School, Osaka, Japan.

References

1 Holmes DR Jr, Vlietstra RE, Smith HC, *et al*. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol* 1984;**53**:77C–81C.

2 Williams DO, Gruentzig AR, Kent KM, Detre KM, Kelsey SF, To T. Efficacy of repeat percutaneous transluminal coronary angioplasty for coronary restenosis. *Am J Cardiol* 1984;**53**:32C–5C.

3 Block PC, Myler RK, Stertzer S, Fallon JT. Morphology after transluminal angioplasty in human beings. *N Engl J Med* 1981;**52**:382–5.

4 Wood WG. Transluminal coronary angioplasty [Letter]. *N Engl J Med* 1982;**306**:1055.

5 Essed CE, van den Brand M, Becker AE. Transluminal coronary angioplasty and early restenosis. Fibrocellular occlusion after wall laceration. *Br Heart J* 1983;**49**:393–6.

6 Saffitz JE, Rose TE, Oaks JB, Roberts WC. Coronary arterial rupture during coronary angioplasty. *Am J Cardiol* 1983;**51**:902–4.

7 Mizuno K, Kurita A, Imazeki N. Pathological findings after percutaneous transluminal coronary angioplasty. *Br Heart J* 1984;**52**:588–90.

8 Waller BF, Gorfinkel J, Rogers FJ, Kent KM, Roberts WC. Early and late morphological changes in major epicardial coronary arteries after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1984;**53**: 42C–7C.

9 Schneider J, Grüntzig A. Percutaneous transluminal coronary angioplasty. Morphologic findings in three patients. *Pathol Res Pract* 1985;**180**:348–52.

10 Giraldo AA, Esposo OM, Meis JM, Intimal hyperplasia as a cause of restenosis after percutaneous transluminal coronary angioplasty. *Arch Pathol Lab Med* 1985;**109**:173–5.

11 Soward AL, Essed CE, Serruys PW. Coronary arterial findings after accidental death immediately after successful percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1985;**56**:794–5.

12 Austin GE, Ratliff NB, Hollman J, Tabei S, Phillips DF. Intimal proliferation of smooth muscle cells as an explanation for recurrent coronary artery stenosis after percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1985;**6**:369–75.

13 Düber C, Jungbluth A, Rumpelt H-J, Erbel R, Meyer J, Thoenes W. Morphology of the coronary arteries after combined thrombolysis and percutaneous transluminal coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 1986;**58**:698–703.

14 Colavita PG, Ideker RE, Reimer KA, Hackel DB, Stack RS. The spectrum of pathology associated with percutaneous transluminal coronary angioplasty during acute myocardial infarction. *J Am Coll Cardiol* 1986;**8**:855–60.

15 Wijns W, Serruys PW, Reiber JHC, *et al*. Early detection of restenosis after successful percutaneous transluminal coronary angioplasty by exercise-redistribution thallium scintigraphy. *Am J Cardiol* 1985;**55**:357–61.

16 MacDonald RG, Feldman RL, Conti CR, Pepine CJ. Thromboembolic complications of coronary angioplasty. *Am J Cardiol* 1984;**54**:916–7.

17 Block PC, Elmer D, Fallon JT. Release of atherosclerotic debris after transluminal angioplasty. *Circulation* 1982;**65**:950–2.

18 Sanborn TA, Faxon DP, Waugh D, *et al*. Transluminal angioplasty in experimental atherosclerosis: analysis for embolization using an in vivo perfusion system. *Circulation* 1982;**66**:917–22.

19 Isner JM, Fortin RV. Frequency in nonangioplasty patients of morphologic findings reported in coronary arteries treated with transluminal angioplasty. *Am J Cardiol* 1982;**51**:689–93.

20 Faxon DP, Sanborn TA, Haudenschild CC, Ryan TJ. Effect of antiplatelet therapy on restenosis after experimental angioplasty. *Am J Cardiol* 1984;**53**: 72C–6C.

21 Steele PM, Chesebro JH, Stanson AW, *et al*. Balloon angioplasty. National history of the pathophysiology response to injury in a pig model. *Circ Res* 1985;**57**:105–12.

22 Austen WG, Edwards JE, Frye RL, *et al*. A reporting system on patients evaluated for coronary artery disease. Report of the ad hoc committee for grading of coronary artery disease, council on cardiovascular surgery, American Heart Association. *Circulation* 1975;**51**(suppl):5–40.

Br Heart J 1987;58:644–52

Percutaneous aortic balloon dilatation for calcific aortic stenosis in elderly patients: immediate haemodynamic results and short term follow up

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SUMMARY Eight elderly patients (mean (SD) age 72·6 (8·5) years) with severe calcified stenosis of the aortic valve were considered for transluminal balloon dilatation in the Thoraxcenter between March and November 1986. In one patient the procedure could not be performed because of technical difficulties. Balloons of increasing diameter (13–25 mm) were successively passed retrogradely from the femoral artery and manually inflated with pressures of 400–600 kPa (4–6 atmospheres). Post-dilatation, there were significant changes in left ventricular pressures (from 237/21 to 204/13 mm Hg), mean systolic gradient (from 66 to 41 mm Hg, systolic aortic flow (from 172 to 202 ml/s, and aortic valve area (from 0·47 to 0·74 cm^2); the cardiac index did not increase significantly (from 2·4 to 2·5 l/min/m^2). One patient developed a pseudoaneurysm at the site of the femoral artery puncture that required surgical repair two months after the procedure; one patient experienced an acute left hemianopia during the procedure but had almost completely recovered at discharge. Five patients maintained a clinical improvement at a mean follow up time of 4·5 months after the procedure; two patients underwent aortic valve replacement, one because of minimal haemodynamic improvement after aortic balloon dilatation and persistence of severe dyspnoea and the other because of late recurrence of symptoms caused by restenosis after a successful procedure.

Aortic balloon dilatation provides an alternative treatment for patients who are poor surgical candidates for cardiac or extracardiac reasons. At this stage the limited haemodynamic improvements suggest that the treatment can only be regarded as palliative, although proposed technical advances may achieve better immediate results in the future. Long term follow up is needed to evaluate the usefulness of this technique.

The poor prognosis of adult patients with symptomatic aortic stenosis has been known for some time: in particular Ross and Braunwald and Frank *et al* showed that patients who develop left ventricular failure have a high yearly mortality.[1 2] An increasing number of studies have reported that aortic valve replacement can be performed with a reasonable operative mortality and encouraging long term survival, even in patients who are >70 years old.[3-5] Although improvements in surgical techniques and postoperative care have lowered the operative mortality rate, associated diseases often make the management of many elderly patients difficult and this has encouraged the development of alternative methods of treatment.

We report the technique and the immediate results and complications of percutaneous aortic balloon dilatation in seven consecutive elderly patients with acquired calcific aortic stenosis.

Patients and methods

CLINICAL DATA

Since March 1986 eight patients (mean (SD) age 74 (8·8), range 63–84; 4 men and 4 women) have been

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considered for percutaneous aortic balloon dilatation. The procedure was performed in only seven patients because one, patient 4, a 84 year old man with severe aortic stenosis, was excluded because he had tortuous iliac and subclavian vessels that made diagnostic haemodynamic evaluation difficult. Table 1 shows the clinical data. Two patients were in functional class II of the New York Heart Association and six were in class III. Five patients had a history of previous angina and three of syncopal attacks. Two patients (cases 6 and 7) had signs of congestive heart failure. Most patients presented with associated cardiovascular (cases 3, 5, 6) or non-cardiovascular diseases (cases 4, 7) or both (case 1).

Patient 6 had previously undergone a mitral valve replacement for severe mixed mitral valve disease. A recent catheterisation had confirmed a well functioning Björk-Shiley prosthesis in the mitral position with severe aortic stenosis (valve area = 0·5 cm^2), and mild pulmonary hypertension (arteriolar pulmonary resistance 262 dyn s cm^{-5}). Two patients (cases 2 and 8) had previously declined aortic valve replacement, and were referred to our centre specifically for percutaneous aortic balloon dilatation. Neither had concomitant disease. Percutaneous aortic balloon dilatation was felt to be justified in all patients because of the relatively high surgical risk associated with advanced age, poor general health, and concomitant diseases.

HAEMODYNAMIC AND ANGIOGRAPHIC DATA

Left ventricular and aortic pressures and mean systolic transaortic gradients were averaged and calculated on line after acquisition periods of 20 seconds. Cardiac output was computed from duplicate thermodilution measurements by a computerised system that also enabled instant calculation of systolic aortic flow and aortic valve area.[6] Table 2 shows the basal haemodynamic data. All patients had a mean systolic gradient >40 mm Hg (in three it was >70 mm Hg) and an aortic valve area $\leq 0·7$ cm^2.

Large, localised areas of aortic valve calcification were detected in all the patients. Mean (SD) left ventricular end diastolic and end systolic volumes, normalised for body surface area, were 81 (10) ml/m^2 and 41 (17) ml/m^2 respectively, left ventricular ejection fraction ranged from 30 to 65% (mean 51%), and left ventricular weight ranged from 136 to 209 g/m^2 (mean 164 g/m^2).

A trace of aortic insufficiency was present in three patients, and there was mild aortic regurgitation in three others. A competent aortic valve was found in one patient.

The aetiology of the aortic valve stenosis was rheumatic in case 6; a presumed degenerative pathogenesis was suspected in the other patients who were ≥ 63 years old and who had late discovery of a cardiac murmur with no previous history of acute rheumatic fever.

BALLOON DILATATION PROCEDURE

After being informed of the possible risks of the procedure all patients gave their informed consent. Percutaneous aortic balloon dilatation was performed in two patients at the time of the diagnostic catheterisation and at a separate session in five patients. A Swan-Ganz thermodilution catheter was positioned in the pulmonary artery via the left femoral vein and a 7F pigtail catheter was placed via the left femoral artery in the ascending aorta.

Before we started percutaneous aortic balloon dilatation, we gave intravenous atropine (1·0 mg) and heparin (5000 IU). One to two units of blood were usually infused to expand the circulating volume. We found that these patients were susceptible to severe hypotension caused by the loss of small amounts of blood associated with the exchange of catheters.

We advanced a left 7F Judkins or Amplatz catheter through the right femoral artery into the ascending aorta just above the aortic cusps and directed its tip towards the jet stream. Thereafter, a straight 0·038 inch guide wire was used to cross the aortic valve. After the basal left ventricular pressures

Table 1 *Clinical data*

Patient	*Age*	*Sex*	*NYHA*	*Angina*	*Syncope*	*Associated diseases*
1	76	M	III	+	+	Diabetes mellitus, nephrolithiasis two-vessel CAD
2	63	M	II	+	–	None
3	64	F	II	+	–	Systemic hypertension, arterial claudication
4	84	M	III	–	+	Chronic obstructive lung disease
5	82	F	III	+	–	Three vessel CAD
6	65	F	III	–	–	Mitral prosthesis
7	83	F	III	+	–	Anaemia, rheumatoid arthritis
8	75	M	III	–	+	None

CAD, coronary artery disease, NYHA, New York Heart Association class

Table 2 *Haemodynamic data before and after aortic valve dilatation in 7 elderly patients*

Patient	*LV*		*Aorta*		*MSG*		*CI*		*AF*		*AA*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	247/24	229/11	191/77	201/84	57	39	2·1	2·5	179	245	0·5	0·9
2	275/31	222/16	177/86	154/66	78	56	3·2	2·6	234	270	0·6	0·8
3	264/15	177/2	198/81	142/73	81	31	2·7	2·7	134	197	0·3	0·8
4	230/16	188/19	157/63	166/63	67	28	2·1	2·6	136	166	0·4	0·7
5	204/23	210/23	150/67	174/83	48	41	1·9	2·1	152	163	0·5	0·6
6	238/12	212/2	133/57	142/71	80	58	2·2	2·0	136	120	0·3	0·4
7	203/28	188/15	156/90	155/87	53	37	2·8	2·8	231	259	0·7	1·0
Mean (SD)	237/21 (28/7)	204/13 (19/8)	166/74 (23/9)	162/75 (21/9)	66 (14)	41 (12)	2·4 (0·5)	2·5 (0·3)	172 (44)	202 (57)	0·47 (0·15)	0·74 (0·20)
	$p<0{\cdot}05$		NS		$p<0{\cdot}005$		NS		$p<0{\cdot}05$		$p<0{\cdot}005$	

AA, aortic area (cm^2); AF, systolic aortic flow (ml/s); CI, cardiac index (l/min/m^2); LV, left ventricular peak systolic and end diastolic pressures (mm Hg); MSG, mean systolic aortic gradient (mm Hg).

and transvalvar gradient had been measured, an exchange 0·038 inch straight guide wire, with its soft tip manually fashioned to a big J shape, was positioned in the left ventricle. With this guide wire left in place, the Judkins catheter was removed and a dilatation catheter was advanced across the aortic valve, after careful removal of the air from the balloon.

The balloon was inflated by hand injection with a mixture of contrast medium and saline (30/70) at pressures of 400–600 kPa (4–6 atmospheres). Initially a balloon of 13–15 mm was used, and after the balloon was in a stable position across the aortic valve (Fig 1) a series of 10–15 seconds inflations were performed. Waisting of the inflated balloon was not usually seen. At the end of each series of dilatations with the same balloon, left ventricular pressure, aortic pressure, cardiac output, systolic aortic flow, and aortic valve area were reassessed. Balloons of increasing diameter were used to reduce the mean transstenotic gradient to <40 mm Hg and to increase the aortic valve area to >1·0 cm^2. If these end points could not be obtained with a 20 mm balloon additional dilatations were performed with a 3 × 12 mm (25 mm) trefoil balloon (Schneider Medintag Zürich). Figure 2 shows the reduction in mean systolic gradient obtained with the conventional 13–20 mm balloons and the additional benefit achieved with the larger balloon. The mean number of balloons used per patient was 3·8 (range 3–6) and the mean number of dilatations per patient was 8·6 (range 6–14). Balloons of two different lengths were used (40 and 80 mm). One trefoil balloon could not be inserted into the femoral artery and five balloons ruptured during the inflations.

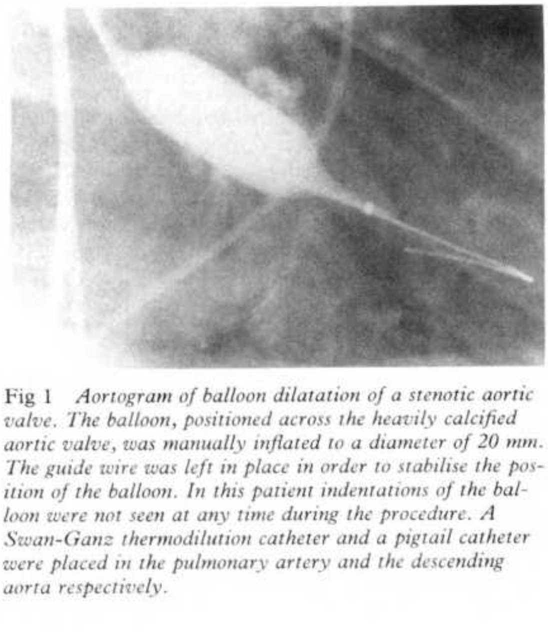

Fig 1 *Aortogram of balloon dilatation of a stenotic aortic valve. The balloon, positioned across the heavily calcified aortic valve, was manually inflated to a diameter of 20 mm. The guide wire was left in place in order to stabilise the position of the balloon. In this patient indentations of the balloon were not seen at any time during the procedure. A Swan-Ganz thermodilution catheter and a pigtail catheter were placed in the pulmonary artery and the descending aorta respectively.*

At the end of the procedure the presence of aortic regurgitation was assessed by supravalvar aortography.

STATISTICAL ANALYSIS

Student's *t* test for paired data was used whenever appropriate.

Results

HAEMODYNAMIC DATA

Table 2 shows the haemodynamic variables measured soon after the last percutaneous aortic balloon dilatation and the same data before dilatation. Statistically significant decreases in peak systolic and end diastolic ventricular pressure, in mean systolic and peak systolic gradient, aortic flow, and valve area were achieved; there was also a slight but not statistically significant increase in cardiac index. Figure 3 shows the aortic valve areas before and after dilatation; all patients had an increase in aortic valve area at the end of the procedure. None the less in three patients the aortic valve area was still ≤0·7 cm^2 after dilatation. Similar improvements were shown when the mean systolic gradient was evaluated (Fig 4): in all but three of the patients a decrease >20 mm

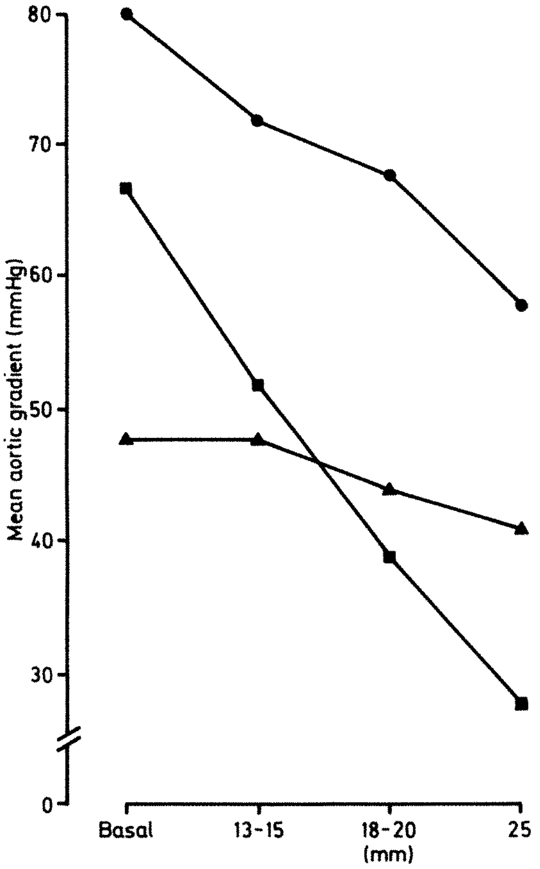

Fig 2 *Mean systolic gradient after successive dilatations with balloons of increasing diameter (13–15, 18–20, and 25 mm) in the three patients who had dilatation with a trefoil balloon showing the additional improvement in gradient achieved with larger balloons.*

Hg was achieved; in these three mean systolic gradients >40 mm Hg were present after dilatation.

AORTIC INSUFFICIENCY

Supravalvar aortography immediately after dilatation showed an increase in aortic regurgitation in four patients, but no patient had more than moderate regurgitation (2+/4+) at the end of the procedure.

COMPLICATIONS

Repeat inflations of the balloon, positioned across the aortic valve were usually well tolerated: in most patients there was a moderate decrease in the aortic pressure, which was continuously monitored during the procedure, but the peak systolic pressure fell to 40 mm Hg in only one (case 8); this was associated with a symptom of dizziness. Patient 5 complained of mild chest pain during and immediately after most of the inflations, with no further ST-segment change. Patient 2 needed surgical repair of a right femoral pseudoaneurysm two months after percutaneous aortic balloon dilatation; in this patient more catheters (six) were used because two balloons ruptured during inflation. In patient 5, a large haematoma developed at the site of balloon insertion in the right groin. Patient 6 experienced considerable hypotension, ST segment elevation, and loss of consciousness immediately after a 25 mm balloon had ruptured during inflation; she recovered completely within three minutes. Despite careful venting of the balloon before insertion, an air embolus was suspected.

A complete left hemianopia was present in patient 3 at the end of the procedure; computerised axial tomography suggested a small infarction in the area supplied by the right posterior cerebral artery. Minor residual defects of the field of vision were still present at discharge.

SHORT TERM FOLLOW UP

We obtained data on clinical follow up (35 days to 8 months, mean 4·5 months). In five patients the clinical improvement (at least by one functional New York Heart Association class) persisted. The other two patients (cases 1 and 6) subsequently underwent

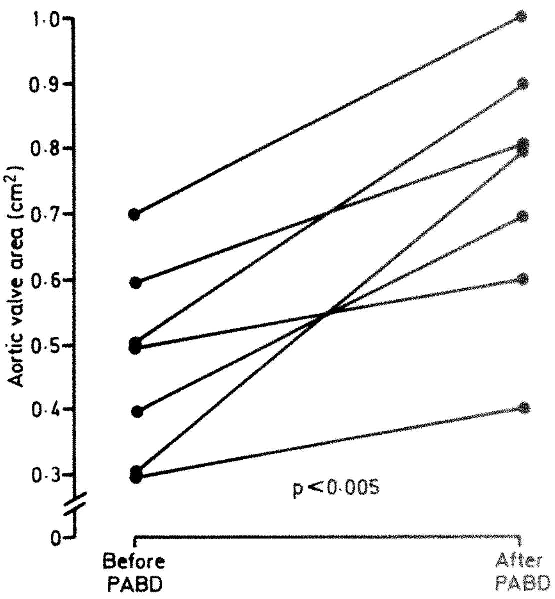

Fig 3 *Aortic valve area before and after dilatation in 7 elderly patients. PABD, percutaneous aortic balloon dilatation.*

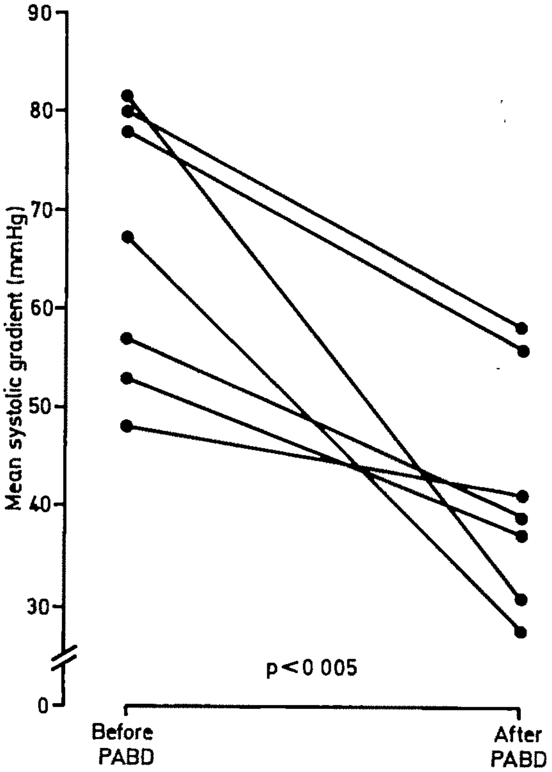

Fig 4 *Mean systolic aortic gradient before and after aortic dilatation in seven elderly patients. PABD, percutaneous aortic balloon dilatation.*

uncomplicated aortic valve replacement. After a successful percutaneous aortic balloon dilatation (aortic valve area increased from 0·5 to 0·9 cm^2) patient 1 experienced considerable functional improvement with disappearance of angina and syncopal attacks for three months, after which there was recurrence of angina and worsening of effort tolerance. Echo-Doppler cardiography showed that the peak aortic flow velocity, which had been reduced from 5 m/s to 2·5 m/s, had increased again to 4·5 m/s. After a syncopal attack, an aortic valve replacement was performed. The native bicuspid valve was diffusely calcified without commissural fusion; there was no tearing of the leaflet edges nor other macroscopic findings that might be related to the previous dilatation. A histological evaluation showed gross calcific deposits with bony degeneration, associated with fragmented areas of calcification, surrounded by connective tissue consisting of young fibroblasts with infiltrating lymphocytes and plasma cells (fig 5). Patient 6 was operated on 40 days after percutaneous aortic balloon dilatation because of the persistence of dyspnoea on minimal effort and at rest: the valve was tricuspid, with partial commissural fusion, diffuse thickening, and isolated nodular calcifications; no macroscopic damage or modifications related to percutaneous aortic balloon dilatation were found. Histological examination showed small areas of combined calcific fragments and fibrous tissue with some plasma cells.

Discussion

An increase in life expectancy and an improvement in the quality of life should not be denied to elderly patients with symptomatic aortic valve stenosis: at present aortic valve replacement is the most effective treatment but operative mortality ranges from 3%[7] to 18%,[8] and higher rates have been reported in patients who are older than 75[9] or who have undergone emergency operation and are in poor general health.[10] Moreover, coexisting cardiac or extracardiac disease may preclude operation.

Balloon dilatation of the aortic valve was introduced in 1983 for young patients with congenital aortic stenosis[11] and only recently applied to cases of severe, calcified aortic valve stenosis in elderly patients.[12]

MECHANISM OF BALLOON DILATATION OF THE AORTIC VALVE

Degeneration of the fibrous stroma of the valves, lipid accumulation, and microscopically identifiable calcifications are common abnormalities in the elderly.[13] In a few cases nodular calcific deposits on the aortic aspects of the cusps result in a critical reduction in the leaflet motility. A triradiate orifice, with lack or near lack of commissural fusion, is usually preserved. Among 111 necropsy specimens analysed by Pomerance, senile, degenerative (Mönckeberg) calcification of the aortic valve accounted for 61% of cases of aortic stenosis in patients aged between 75 and 85 years and for nearly all patients older than 85 years.[14] The next most frequent finding in patients over 75 years of age and the commonest finding in younger patients, with a peak incidence occurring in the fifth and sixth decades,[15] was degenerative calcification in congenitally bicuspid aortic valves: a transverse or slightly crescentic slit-like orifice, extending completely across the aortic lumen, was usually seen. Occasionally an inflammatory (rheumatic) pathogenesis is present in elderly patients[16] and heavily calcified commissures are the most common finding in such patients.

In contrast with reports of dilatation in pulmonary and mitral valve stenosis,[17] where separation of the fused commissures results in haemodynamic improvement, the pathogenesis of the aortic stenosis

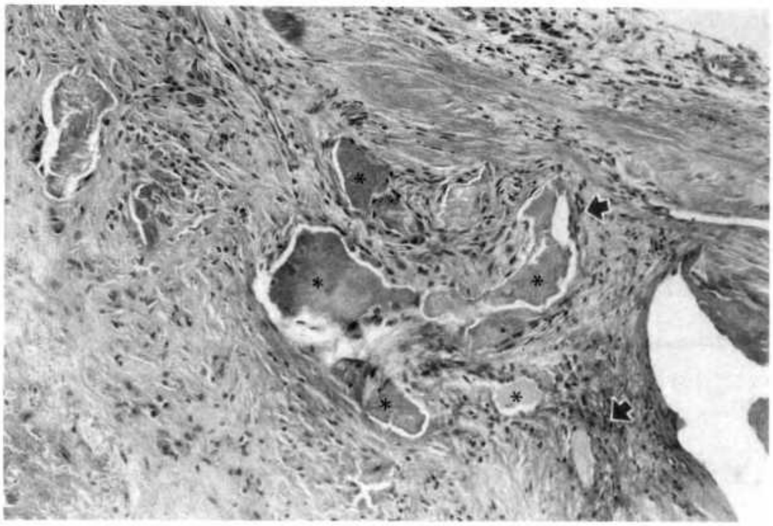

Fig 5 *Photomicrograph of a restenosed bicuspid aortic valve replaced 5 months after aortic balloon dilatation (haematoxylin and eosin stain; original magnification × 100). Particles of calcium (*) were embedded in the valve tissue and were surrounded by scar tissue consisting of young fibroblasts and infiltrating lymphocytes and plasma cells (arrows).*

in the elderly suggests that cusp separation does not have a major role. McKay *et al* recently performed postmortem or intraoperative percutaneous aortic balloon dilatation in 10 patients with an average age of 78 years: successful dilatation was related to a simple plastic deformation of the valve cusps in most patients, while fracture of heavy nodular calcifications and separation of fused commissures were less common findings.[18] Similar findings have recently been reported by Reynolds *et al*.[19] Vahanian *et al*, who performed postmortem dilatation in 22 bicuspid and tricuspid aortic valves, suggested that the mechanisms of percutaneous aortic balloon dilatation could be related to "an improvement in cusp motion due to calcium redistribution".[20]

SAFETY OF DILATATION

Potential risks of percutaneous aortic balloon dilatation include damage to the peripheral vessels during insertion of multiple, stiff balloon catheters (ranging from 8 to 9F), occlusion of the aortic flow during balloon inflations, peripheral embolisation because calcific tissue is dislodged, and massive aortic insufficiency caused by gross tearing of the leaflets or to detachment of the cusps from the aortic ring.

Although extreme tortuosity and severe atherosclerosis of the peripheral vessels are often seen in patients of advanced age, correct positioning of the dilatation catheter via the femoral route was possible in seven of our eight patients. One late pseudoaneurysm of the common femoral artery required surgical repair.

Total occlusion of the aortic valve may induce a potentially dangerous rise in left ventricular pressure. To minimise this problem, an arteriovenous shunt was used during the first reported attempts of percutaneous aortic balloon dilatation in children.[11] Our experience and the experience of others[12] in elderly patients suggests that a residual flow is still present during balloon inflation; in six patients with calcified stenosis of the aortic valve no severe reduction of the arterial pressure was observed and only one patient experienced angina during the inflations.

Figure 6 summarises the haemodynamic findings during a three minute balloon inflation.[21] This shows that there was no significant increase in intraventricular pressure and only a moderate decrease in arterial pressure and aortic flow. These observations and the frequent absence of evident waisting of the balloon during inflation suggest that the stiffness of the cusps and the non-circular configuration of the orifice prevent the complete adherence of the leaflets to the balloon and consequently avoids total valve occlusion, unlike the reported findings during pulmonary and aortic dilatations in the young where sudden orifice occlusion may produce abrupt haemodynamic changes.

Calcific stenosis of the aortic valve was regarded as a contraindication to percutaneous aortic balloon

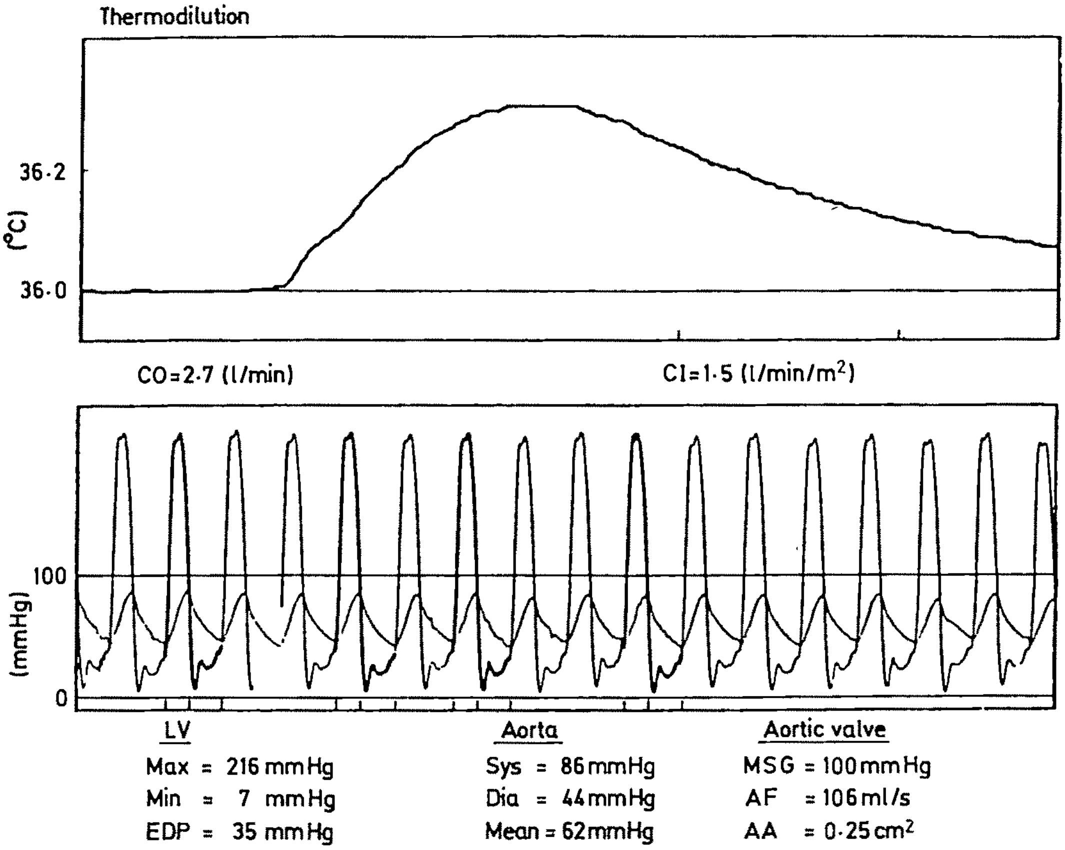

Fig 6 *Cardiac output (thermodilution method) and left ventricular and aortic tracings during balloon inflation across the aortic valve; the balloon (diameter 20 mm) was inflated for 3 minutes without subjective complaints. AA, aortic area; AF, systolic aortic flow; CI, cardiac index; CO, cardiac output; EDP, left ventricular end diastolic pressure; LV, left ventricle; MSG, mean systolic transaortic gradient.*

dilatation when this technique was introduced.[22] To date two embolic complications have been reported[23 24] and the potential danger of peripheral embolisation cannot be ignored. In our series patient 3 had a small cerebral infarction, probably caused by a calcific embolus, with minor persistent functional damage.

None of our patients had a potentially dangerous increase in aortic insufficiency after percutaneous aortic balloon dilatation; nevertheless, at present percutaneous aortic balloon dilatation cannot be recommended in patients with greater than mild coexistent aortic insufficiency.

IMMEDIATE RESULTS OF DILATATION

McKay *et al* reported an increase in aortic valve area from 0 6 to 1·0 cm² in 10 elderly patients[25] while Jackson *et al* obtained a mean reduction greater than 50% in peak systolic gradient in eight patients.[26] The mean (SD) aortic area was increased from 0·45 (0·18) to 0·81 (0·36) cm² in 158 patients collected by the French Registry.[24] Comparable results were achieved in our patients (aortic valve area increased from 0·47 to 0·74 cm²) but a severely reduced absolute aortic valve area (≤0·7 cm²) persisted in three patients. We calculated the aortic valve area on the basis of mean gradient (planimetry of the area enclosed between simultaneously recorded left ventricular and aortic pressure tracing).

The lack of a considerable immediate improvement in some of our patients may be related to the anatomy of the aortic valve (percutaneous aortic balloon dilatation was partially unsuccessful in the patient with rheumatic aortic stenosis) or to inadequate balloon diameters (in three patients with unsuccessful haemodynamic improvements after repeated inflations of conventional 13–20 mm balloons we achieved better results using a 3 × 12 mm (25 mm) trefoil balloon). The use of balloons 2–3 mm smaller than the aortic annulus has been proposed in children to reduce the development of aortic regurgitation.[27] The fear of gross tearing of the calcific leaflets or of their detachment from the aortic ring, with consequent massive aortic insufficiency, or of disruption of the aortic ring itself has resulted in even more caution in adult patients. In the reports of McKay *et al*,[25] Jackson *et al*[26] and Cribier *et al*[24] the largest balloon sizes used were 20, 14, and 21 mm respectively. Postmortem and intraoperative data, however, suggest that larger balloons are needed for valves without commissural fusion or heavy nodular calcification.[18]

EARLY FOLLOW UP

Major functional improvements can be expected as a consequence of even relatively small increases in valve area, as has recently been reported in most patients after percutaneous aortic balloon dilatation.[28] Five of our seven patients obtained persistent functional improvement, while two patients needed subsequent aortic valve replacement: in one of them a restenosis three months after percutaneous aortic balloon dilatation caused the late recurrence of symptoms and serial Doppler assessment showed increasing aortic flow velocity. In paediatric patients no increase in aortic stenosis was reported 3–9 months after percutaneous aortic balloon dilatation,[29] but rates of increase in peak systolic gradient as high as 3–4 mm Hg per month were described in adult patients with aortic stenosis.[30] The lack of information on long term benefits after percutaneous aortic balloon dilatation necessitates a strict control programme.

Calcification surrounded by fibrous tissue can be found in aortic valves with stenosis of various aetiologies as well as in non-stenotic, sclerotic valves in the elderly. In our first patient, who was operated on five months after percutaneous aortic balloon dilatation because symptoms recurred, histology of the aortic valve suggested that a scarring process adjacent to the fragmented calcification was the mechanism of late restenosis.

Currently aortic dilatation provides effective palliative treatment in many patients with severe aortic stenosis, although it remains to be determined whether more definitive long term benefit can be expected. Further observations are needed to assess the efficacy and safety of the procedure (particularly when larger diameter balloons are used) as well as the progression of valve disease after dilatation.

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References

1 Ross J Jr, Braunwald E. Aortic stenosis. *Circulation* 1968;**38** V:61–7.
2 Frank S, Johnson A, Ross J Jr. Natural history of valvular aortic stenosis. *Br Heart J* 1973;**35**:41–6.
3 Jamieson WRE, Dooner J, Munro IA, *et al.* Cardiac valve replacement in the elderly: a review of 320 consecutive cases. *Circulation* 1981;**64 II**:177–83.
4 Arom KV, Nicholoff DM, Lindsay WG, Northrup WF, Kersten TE. Should valve replacement and related procedures be performed in elderly patients? *Ann Thorac Surg* 1984;**38**:466–72.
5 Storstein O, Efskind L. Aortic valve replacement in elderly patients. *Acta Med Scand* 1979;**206**:161–4.
6 Meester GT, Bernard N, Zeelenberg C, Brower RW, Hugenholtz PG. A computer system for real-time analysis of cardiac catheterization data. *Cathet Cardiovasc Diagn* 1975; **1**:113–32.
7 Hochberg MS, Morrow AG, Michaelis LL, McIntosh CL, Redwood DR, Epstein SE. Aortic valve replacement in the elderly. *Arch Surg* 1977;**112**:1475–80.
8 Quinlan R, Cohn LH, Collins JJ Jr. Determinants of survival following cardiac operations in elderly patients. *Chest* 1975;**68**:498–500.
9 Cabrol C, Gandjbakhch I, Pavie A. La chirurgie de remplacement valvulaire. In: Acar J, ed. *Cardiopathies valvulaires acquises*. Paris: Flammarion Médicine-Sciences, 1985:513–46.
10 Glock Y, Pecoul R, Cerene A, Laguerre J, Puel F. Aortic valve replacement in elderly patients. *J Cardiovasc Surg* 1984;**25**:205–10.
11 Lababidi Z. Aortic balloon valvuloplasty. *Am Heart J* 1983;**106**:751–2.
12 Cribier A, Saoudi N, Berland J, Savin T, Rocha P, Letac B. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? *Lancet* 1986;**i**:63–7.
13 Pomerance A. Pathology of the myocardium and valves. In: Caird FI, Dall JLC, Kennedy RD, eds. *Cardiology in old age*. New York: Plenum Press, 1976:11–55.
14 Pomerance A. Pathogenesis of aortic stenosis and its relation to age. *Br Heart J* 1972;**34**:569–74.
15 Fenoglio JJ Jr, McAllister HA Jr, DeCastro CM, Davia JE, Cheitlin MD. Congenital bicuspid aortic valve after age 20. *Am J Cardiol* 1977;**39**:164–9.
16 Roberts WC, Perloff JK, Costantino T. Severe valvular aortic stenosis in patients over 65 years of age. A clinicopathologic study. *Am J Cardiol* 1971;**27**:497–506.
17 Inoue K, Owaki T, Nakamura T, Kitamura F, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984;**87**:394–402.
18 McKay RG, Safian RD, Lock JE, *et al.* Balloon dilatation of calcific aortic stenosis in elderly patients: postmortem, intraoperative, and percutaneous valvuloplasty studies. *Circulation* 1986;**74**:119–25.
19 Reynolds DJM, Stone DL, Wells FC, Petch MC. How does aortic balloon valvuloplasty work? [Abstract.] *Br Heart J* 1987;**57**:70.
20 Vahanian A, Guérinon J, Slama M, Griveaux M, Acar J. Experimental balloon valvuloplasty of

calcified aortic stenosis in the elderly [Abstract.] *Circulation* 1986;74 II:365.

21 Serruys PW, de Feyter PJ, van den Brand M. Percutaneous transluminal valvuloplasty of a narrowed aortic valve. A case report. *Hart Bull* 1986;6:171–6.

22 Walls JT, Lababidi Z, Curtis JJ, Silver D. Assessment of percutaneous balloon pulmonary and aortic valvuloplasty. *J Thorac Cardiovasc Surg* 1984;88:352–6.

23 Starkey IR, Cumberland DC, Oakley GDG. Balloon aortic valvuloplasty for severe calcific aortic stenosis: effective but not without hazards [Abstract.] *Br Heart J* 1987;57:69.

24 Cribier A, Letac B, Lancelin B, *et al.* Percutaneous balloon valvuloplasty (PBV) for acquired aortic stenosis: preliminary immediate results of the French Registry [Abstract]. *Circulation* 1986;74 II:208.

25 McKay RG, Safian RD, Lock JE, *et al.* Percutaneous balloon valvuloplasty in elderly patients with calcific aortic stenosis [Abstract]. *Circulation* 1986;74 II:207.

26 Jackson G, Thomas S, Monaghan M, Forsyth A, Jewitt D. Inoperable aortic stenosis in the elderly: benefit from percutaneous transluminal valvuloplasty. *Br Med J* 1987;294:83–6.

27 Choy M, Beekman RH, Crowley DC, Rocchini AP. Balloon dilatation in infants and children with valvular aortic stenosis [Abstract]. *J Am Coll Cardiol* 1986;7:117A.

28 Cribier A, Savin T, Saoudi N, Behar P, Rocha P, Letac B. Percutaneous balloon valvuloplasty (PBV) in adult aortic stenosis: an alternative to surgery for valve replacement [Abstract]. *Circulation* 1986; 74 II:365.

29 Lababidi Z, Jiunn-Ren WU, Walls JT. Percutaneous balloon aortic valvuloplasty: results in 23 patients. *Am J Cardiol* 1984;53:149–97.

30 Cheitlin MD, Gertz EW, Brundage BH, Carlson CJ, Quash JA, Bode RS. Rate of progression of severity of valvular aortic stenosis in the adult. *Am Heart J* 1979;98:689–700.

Br Heart J 1987;58:653–8

Congenital heart malformations in Jutland, Denmark: a three year necropsy study in children aged 0–14 years

Epidemiology and classification according to sequential segmental analysis

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SUMMARY The use of sequential segmental analysis for describing congenital heart malformations was the method of assessment used in a prospective necropsy study covering Jutland, a well defined geographical and demographic area of Denmark. The study group was 1154 children of whom 261 (22·6%) had a congenital heart malformation. The most common malformations were ductus arteriosus and ventricular septal defect and there were 77 cases in which connections between chambers or between chambers and great arteries were anomalous (68 liveborn; 37 male and 31 female: nine stillborn; two male and seven female). No difference in sex distribution or seasonal variation was found between those with congenital heart disease and those without. Extracardiac malformations and chromosomal abnormalities were more often seen in children with congenital heart malformation than in those without (30·3% *vs* 16·6%).

The sequential segmental analysis is a logical and precise way of describing congenital heart malformations and it should be routinely used to classify cases of congenital heart malformation.

Difficulties with the use of nomenclature in the routine management of paediatric cases of congenital heart disease prompted us to test a system of nomenclature based upon identification of segmental connections that was proposed by Shinebourne *et al* in 1976.[1]

We present a necropsy study of congenital heart malformations collected prospectively in a well-defined geographical and demographic area of Denmark in which necropsy is often performed.

Patients and methods

The children included in the study died between 1 January 1977 and 31 December 1979. They were 0–14 years old or were stillbirths weighing ≥ 1000 g. The cases were collected prospectively and without selection. During the study period there were 91 531 livebirths and 521 registered stillbirths. Officially the gestational age of a stillbirth is 28 weeks, but we chose to use birthweight as an inclusion criterion because it is more accurate and convenient. Jutland (fig 1), is a demographically well-defined part of Denmark with a population of 2 313 034 (1 January 1978). Jutland is divided into seven counties and we obtained separate results for these to investigate whether there were geographical differences.

All ten departments of morbid anatomy and two institutes of forensic medicine serving the area were informed of the study by letter and orally. Written consent was obtained from the departments. Every few months we sent them written reminders. Our tracing rate for collecting specimens and data was cross-checked against the files of the National Health Board, to which all deaths, including stillbirths, are reported. This meant that we could also trace children who were born in the area of study but who died outside it.

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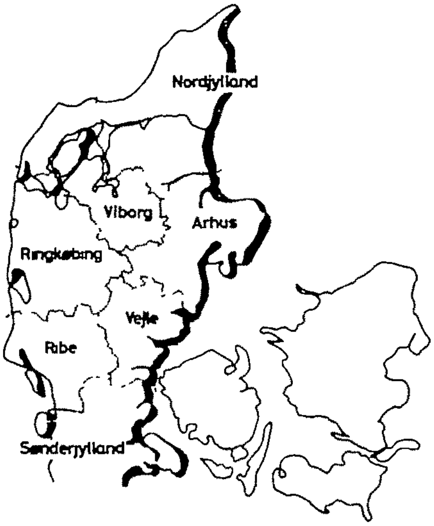

Fig 1 *Jutland (7 counties).*

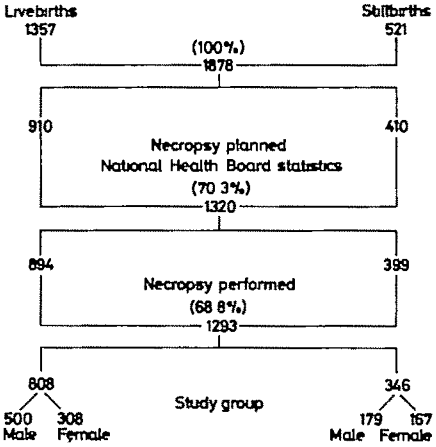

Fig 2 *Selection of study population.*

During the study period 1357 children aged 0–14 years died and there were 521 registered stillbirths (a total of 1878 children). The statistics of the National Health Board showed that necropsy was planned in 1320 cases (70·3%) and performed in 1293 cases (68·8%). We studied 1154 (61·4%) cases (fig 2).

A forensic necropsy was performed in 133 cases (11·5%), which were mainly cot deaths. The remaining 1021 necropsies were performed at the request of the hospital. We personally investigated heart-lung preparations or the entire organ block in 894 (77·5%). In 260 cases (22·5%) we went through the necropsy notes and contacted the pathologists who performed the necropsy.

The method of investigation was the sequential segmental analysis.[1 2] Probe patency of the foramen ovale and patency of the ductus arteriosus beyond one month of age were regarded as definite heart malformations. In children < 1 month of age or in stillbirths these findings were not categorised as heart malformations.

In each case a questionnaire was prepared for electronic data processing. The statistical tests that we used are stated in the text. Types and constellations of malformations have been listed by number only.

Results

EPIDEMIOLOGY

We studied 808 (70%) livebirths and 346 (30%) stillbirths. There were 500 liveborn boys (61·9%) and 308 girls (38·1%) and 179 stillborn boys (51·7%) and 167 girls (48·3%) (fig 2).

The frequency of necropsy varied considerably in the seven counties (table 1). According to the National Health Board the mean frequency of necropsy was 68·8%. Our 1154 necropsies represent 90·3% of livebirths and 86·7% of stillbirths (tracing rate). Two hundred and sixty one children (22·6%) had a congenital heart malformation (fig 3a and b) (40 stillbirths (15·3%) and 221 livebirths (84·7%)). The frequency of congenital heart malformation was 21·6% in boys and 24% in girls (χ^2 test = 0·88, $p > 0·3$). Congenital heart malformation was more

Table 1 *Frequency of necropsy and our tracing rate in seven counties*

	Stillbirths		*Livebirths*	
County	*Necropsies/deaths (frequency %)*	*Tracing rate (%)*	*Necropsies/deaths (frequency %)*	*Tracing rate (%)*
Nordjylland	87/96 (90·6)	87/87 (100)	218/270 (81·0)	205/218 (94·0)
Århus	122/145 (84·1)	91/122 (74·6)	209/323 (64·7)	195/209 (93·3)
Viborg	25/58 (43·1)	22/25 (88·0)	73/121 (60·3)	64/73 (87·7)
Ringkøbing	25/50 (50·0)	24/25 (96·0)	96/164 (58·5)	90/96 (93·8)
Ribe	52/53 (98·1)	52/52 (100)	83/130 (63·8)	69/83 (83·1)
Sønderjylland	50/63 (79·4)	32/50 (64·0)	96/157 (61·1)	77/96 (80·2)
Vejle	38/56 (67·9)	38/38 (100)	119/192 (62·0)	108/119 (90·8)
Mean	399/521 (76·6)	346/399 (86·7)	894/1357 (65·9)	808/894 (90·3)

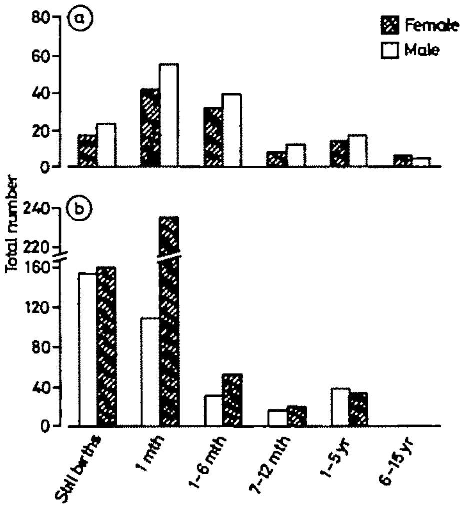

Fig 3 *Age and sex distribution of children (a) with congenital heart disease (b) without congenital heart disease.*

common in livebirths than stillbirths (27·4% *vs* 11·6% (χ^2 test = 34·49, $p < 0·0005$)). The frequency of congenital heart malformation was 24·8% and 31·5% among liveborn boys and girls respectively, and 12·8% and 10·2% for stillbirths. The sex difference for livebirths is statistically significant (χ^2 test = 4·28, $p < 0·05$) but not for stillbirths (χ^2 test = 0·59, $p > 0·4$).

The forensic necropsies showed that 23 children (17·3%) had a congenital heart malformation. These cases constituted 8·8% of all children with a congenital heart malformation.

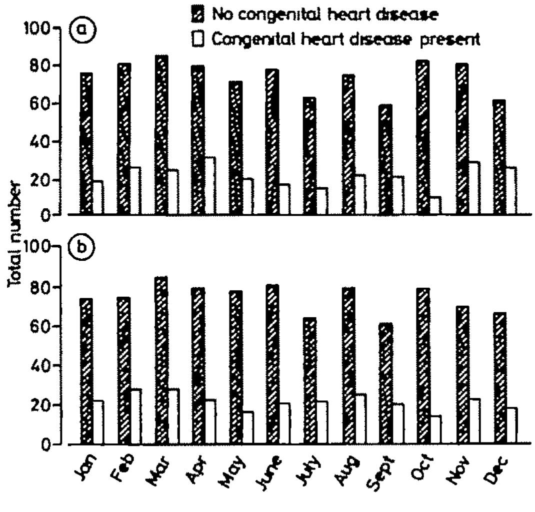

Fig 4 *(a) Month of birth and (b) month of death of study group.*

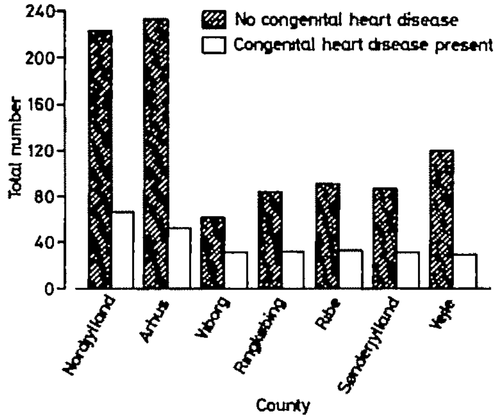

Fig 5 *Distribution of all children in necropsy study according to county.*

Forty children had probe patency persisting beyond one month of age as the only malformation. Births of children with and without congenital heart malformation were equally distributed throughout the year (χ^2 test = 7·34, 11 degrees of freedom, $p > 0·7$), as were deaths (χ^2 test = 11·16, 11 degrees of freedom, $p > 0·1$) (fig 4a and b).

Figure 5 shows the frequency of congenital heart malformation in different counties. There was no geographical variation in the rates of congenital heart malformation within Jutland (χ^2 test = 5·71, six degrees of freedom, $p > 0·4$).

Fifty three children had been operated upon because of congenital heart malformation. The majority (79%) had died less than one month after the operation (table 2).

Two hundred and twenty seven (19·9%) of all children had an extracardiac malformation (129 boys and 98 girls). The frequency of an extracardiac malformation was 19% among boys and 20·6% among girls (χ^2 test = 0·41, $p > 0·4$). Seventy nine (63 livebirths and 16 stillbirths) had a congenital heart malformation as well.

Extracardiac malformations were significantly

Table 2 *Time from operation to death in 53 children operated on for congenital heart disease*

Period	*Died*
During operation	8
< 1 week	34
1–4 weeks	5
1–12 months	5
> 1 year	1
Total	53 (25 girls/28 boys)

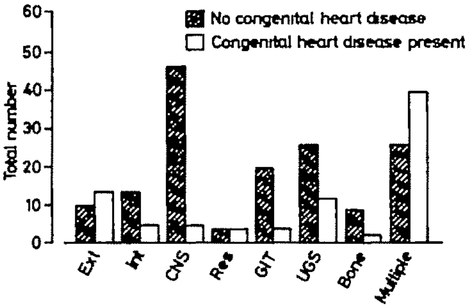

Fig 6 *Extracardiac malformations in children with and without congenital heart disease. Ext, external (non-specified); Int, internal (non-specified); CNS, central nervous system; Res, respiratory system; GIT, gastrointestinal tract; UGS, urogenital system.*

more frequent in those with congenital heart disease (30·3%) than in those without (16·6%) (fig 6) (χ^2 test = 24·27, $p < 0·0005$). More than one other malformation was usually found in children with congenital heart disease. Twenty three children had

Table 3 *Chromosomal abnormalities in study group*

Abnormality (syndrome)	*Total number*	*With congenital heart malformation*	
		Livebirths	*Stillbirths*
Down's syndrome	13 M	9	2
	10 F	7	0
Trisomy 18	3 M	1	1
	6 F	6	0
Trisomy 18 mosaicism	1 M	0	0
Trisomy 13	2 M	1	0
	2 F	2	0
Interstitial deletion of short arm of chromosome 7	1 M	1	0

Table 4 *Specific abnormalities in all children irrespective of chamber connections*

Abnormality	*Livebirths*		*Stillbirths*	
	F	*M*	*F*	*M*
Abnormalities of pulmonary veins.				
Supradiaphragmatic drainage	1	7		
Infradiaphragmatic drainage				4
Abnormalities of systemic veins				
Persistent superior vena cava	6	2		2
Others	2	1		1
Cor triatriatum.				
Left				
Right	1			
Atrial septal defect	36	40	5	8
Probe patency*	40	61	12	15
Ventricular septal defect	48	43	10	14
Atrioventricular valve abnormalities				
Mitral	9	9		1
Tricuspid	1	6		
Both	1	1		
Atrioventricular septal defects	6	9		2
Hypoplasia of ventricles:				
Left	4	11	1	
Right			1	
Ventricular outlet tract:				
Subvalvar aorta/pulmonary artery	0/4	1/5		0/1
Valvar aorta/pulmonary artery	14/18	23/18	2/3	1/3
Supravalvar aorta/pulmonary artery†	4/5	3/6	1/1	
Fallot's tetralogy‡	5	10	1	
Abnormalities of aortic arch:				
Coarctation	13	12	1	2
Other	8	9	2	2
Abnormalities of systemic arteries	2	6		1
Abnormalities of pulmonary trunk and arteries	6	9	1	2
Patent ductus arteriosus*	51	71	16	20

*Probe patency or persistent ductus arteriosus or both in stillbirths were recorded only in combination with other heart malformations.

†These cases include membranes and hypoplastic arteries.

‡In Scandinavia and Germany this abnormality is known as Steno-Fallot's. Niels Stensen (1638–86), Danish anatomist, geologist, and theologian

Table 5 *Data on cases of double inlet ventricles and absence of atrioventricular connection*

	Livebirths		*Stillbirths*	
	F	*M*	*F*	*M*
Right atrial isomerism.				
Double inlet + common atrioventricular valve				
Univentricular heart left type + rudimentary chamber, double outlet + pulmonary stenosis	1			
Univentricular heart indeterminate type, single outlet + rudimentary pulmonary artery		1		
Double inlet univentricular heart				
Left type + rudimentary chamber. Two atrioventricular valves, double outlet		1		
Indeterminate type. Two atrioventricular valves, double outlet		1		
Indeterminate type Common atrioventricular valve, single outlet, common arterial truncus	1			
Absent right atrioventricular connection:				
Univentricular heart left type + rudimentary chamber, single outlet aorta + rudimentary pulmonary artery		1		
Univentricular heart indeterminate type, single outlet, common arterial truncus		1		
Absent left atrioventricular connection:				
Univentricular heart, right type + rudimentary chamber				
single outlet pulmonary artery + aorta rudimentary	1	1		
double outlet	1			
Univentricular heart, indeterminate type.				
single outlet pulmonary artery + aorta rudimentary	1			
double outlet	2			1

Table 6 *Cases of abnormal connections of chamber to chamber and to great arteries in study group*

Abnormality	Livebirths F	Livebirths M	Stillbirths F	Stillbirths M
Juxtaposition of atria.				
Left		1		
Right		1		
Visceroatrial situs:				
Inversus	1		1	
Isomerism (ambiguous)*	1	1		
Atrioventricular connection.				
Discordant	1	1		
Double inlet	2	3		
Absent atrioventricular connection:				
Right		2		
Left	5	1		1
Ventriculoatrial connection				
Discordant	8	7		
Double outlet	7	7		3
Single outlet truncus arteriosus	7	3		2
Single outlet aorta + rudimentary pulmonary artery			2	1
Single outlet pulmonary artery + aorta rudimentary	2	1		

*Two cases of right isomerism with asplenia.

Down's syndrome and of these 18 (78%) had congenital heart malformation. Syndromes other than Down's were found in 15 children (1·3% of the entire study group), and 12 children (80%) had congenital heart malformations.

The congenital heart malformation was estimated to be the cause of death or the major contributing factor of death in 181 (82%) of 221 livebirths.

CLASSIFICATION ACCORDING TO SEQUENTIAL SEGMENTAL ANALYSIS

In the tables we have concentrated on giving the numbers of specific anomalies with normal and abnormal chamber connections and with abnormalities of the great arteries (tables 4–6). Thus an individual patient often appears several times. Furthermore, we have counted and listed separately abnormalities of the coronary arteries (origin or number), anomalies of the coronary sinus, pericardial malformations, and congenital fibroelastosis of the newborn (table 7).

Table 7 *Other congenital heart abnormalities*

Abnormality (of)	Livebirths F	Livebirths M	Stillbirths F	Stillbirths M	Combined with other heart "abnormalities"
Coronary artery*	5	2			5
Coronary sinus†	1	3		1	5
Endocardium (fibroelastosis)‡	2	9			11
Pericardium (defects)			2	1	3
Ebstein's		1			1
Aneurysm of patent ductus arteriosus		1			1
Congenital atrioventricular block	1				1

*Common origin (one ostium) 3; both ostia in one sinus 2; left coronary artery from pulmonary artery 1; missing circumflex artery 1

†Stenosis 1; atresia 4.

‡Hypoplastic left ventricle syndrome not included

Discussion

The death rate in the study population was 1·5%, and 521 stillbirths were registered during the study period. Necropsies were performed in 68·8% and of these 89·2% were investigated by us. There are at least two explanations why we were unable to assess all cases: (*a*) not all cases were referred to us by the primary departments (failure of communication) and (*b*) the official records of the National Health Board are not exhaustive.

Most studies of congenital heart malformation have been restricted to a category of congenital heart malformation or they have been population studies of both live and dead children. Some investigators have examined the frequency of various disorders by analysing museum collections of congenitally malformed hearts thus expressing the frequency of a malformation by relating it to other abnormalities. Our results cannot be compared with such studies.

Our study was conducted at the end point of the disease process. The congenital heart malformation was regarded as the cause of death or the major contributing factor of death in 181 (82%) of 221 liveborn cases. In a detailed study Šámánek *et al* found that congenital heart malformations were a major contributing factor in about 50% of deaths.[3]

About 0·6–0·8% of neonates have a congenital heart malformation.[3] The dead children aged 0–14 years that we studied are equivalent to 0·27% of the total number of infants born in the study period. Among the children aged 0–14 years who died congenital heart malformation was common (22·6% of investigated cases) and was the cause of death in 18% of children.

We have found one necropsy study which we think may be compared with our investigation.[4] Because the grouping of patients is different only parts of the two studies can be compared. In a study of stillbirths and livebirths aged up to one year Wilson and Lubschez found congenital heart malformation in 6%[4] whereas we found 22·6% in our study. The reasons for this discrepancy are not apparent. Gibson reported a frequency of 12% of congenital heart malformation in 1633 necropsies from the Great Ormond Street Clinic,[5] and Nestor and Rice 20% among 675 necropsies.[6] In Gibson's study the age of cases is not given and Nestor and Rice's study did not include stillbirths. The age range in Nestor and Rice's study is, however, identical with ours (0–14 years) and the results are in the same range (20% *vs* 27% in our study after the exclusion of stillbirths from our study). Recent studies of cardiac malformations in spontaneous abortions by Gerlis[7] and Ursell *et al*[8] cannot be compared with our study as they deal with aborted fetuses of <24 or 28 weeks' gestation (which for all practical purposes are fetuses with a birth weight below 1000 g).

Although our study is quite large some of the groups of anomalies are too small for valid statistical analysis; however, some trends are apparent in the new data. The tables that we constructed to show which malformation appeared with other abnormalities have been omitted because they are too complicated to read.

Some solitary anomalies occurred but combinations of malformations were more common. There were only 24 cases of isolated ventricular septal defects (livebirths: five boys, and seven girls; stillbirths: nine boys and three girls), 19 patients with isolated atrial septal defects (livebirths: eight boys and four girls; stillbirths: three boys and four girls), and 14 with persistent ductus arteriosus (five boys and nine girls; stillbirths were not included).

The aim of the study has been to demonstrate the use of the sequential segmental analysis as a routine method of describing congenital heart abnormalities. We found that sequential segmental analysis is a logical and convenient approach and one which because of its stepwise structure ensures a thorough investigation. Although there was considerable discussion about some cases, none of them was unclassifiable by this analysis. We believe that sequential chamber analysis is the method of choice for describing congenital heart malformations.

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References

1 Shinebourne EA, Macartney FJ, Anderson RH. Sequential chamber localization-logical approach to diagnosis in congenital heart disease. *Br Heart J* 1976;38:327–40.

2 Becker AE, Anderson RH. *Pathology of congenital heart disease.* (In: Crawford T, ed. Postgraduate pathology series.) London, Boston, Sydney, Wellington, Durban, Toronto: Butterworths, 1981.

3 Sămánek M, Goetzová J, Benešová D. Causes of death in neonates born with a heart malformation. *Int J Cardiol* 1986;11:63–74.

4 Wilson MG, Lubschez R. Prognosis for children with congenital anomalies of the heart and central vessels. Life expectancy in patent ductus arteriosus. *J Pediatr* 1942;21:23–30.

5 Gibson WM. A survey of the post-mortem findings in 200 cases of congenital heart disease. *Gr Ormond Str J* 1956;11:69–75.

6 Nestor JO, Rice EC. Heart disease in children. *Med Ann Distr Columbia* 1956;25:616–7.

7 Gerlis LM. Cardiac malformations in spontaneous abortions. *Int J Cardiol* 1985;7:29–43.

8 Ursell PC, Byrne JM, Strobino BA. Significance of cardiac defect in the developing fetus: a study of spontaneous abortuses. *Circulation* 1985;72:1232–6.

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A genetic marker for rheumatic heart disease

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SUMMARY The frequency of antigen types (A, B, C, and DR) in an unselected group of 25 patients with chronic rheumatic heart disease and an unselected group of 15 patients with acute rheumatic fever was compared with that in a group of 100 healthy volunteers. All patients and controls were Arabs of Saudi origin. Only the frequency of HLA-DR4 was significantly different in the controls and the patient groups—controls 12%, chronic rheumatic heart disease 72%, acute rheumatic fever 53%, both patient groups together 65% (relative risk 13·6 with 95% confidence interval 10·5–16·7). Eighty three per cent of 12 patients with mitral stenosis and 70% of seven with aortic incompetence had HLA-DR4 antigen. In 17 non-Saudi Arab patients who had acute rheumatic fever or chronic rheumatic heart disease, the frequency of HLA-DR4 was identical (65%) to that in Saudi patients.

These findings may have implications for the pathogenesis of rheumatic fever and rheumatic heart disease.

It has long been suggested that genetic factors contribute towards a predisposition to rheumatic fever and rheumatic heart disease.[1] Though several studies of HLA types have been undertaken none has conclusively shown a marker for such a predisposition. Caughey *et al* found an increase in frequency of HLA-A3 and HLA-A8 and a decrease in frequency of HLA-A10 in 50 Maori patients with rheumatic fever and rheumatic heart disease.[2] Falk *et al*, however, found that a decrease in HLA-A3 was the only difference between white patients and controls.[3] These and other similar studies[4] did not contain data on the HLA-DR antigen. None the less, this is the antigen that is likely to be important in disorders mediated by an abnormal immunological response.[5]

We have re-examined the possible role of HLA antigens, in particular the DR antigens, in predisposing individuals to rheumatic fever and its complications.

Patients and methods

Only patients with acute rheumatic fever that fulfilled the Ducket Jones criteria[6 7] or chronic rheumatic valvar heart disease were studied. Chronic disease was diagnosed in patients aged 12–60 years with clinical and echocardiographic evidence of either stenosis or regurgitation of both the mitral and aortic valves and a history suggestive of rheumatic fever. Those with no history of rheumatic fever or with only one affected valve were excluded from the study.

We studied consecutive outpatients or inpatients attending the rheumatic fever and medical clinics and medical wards of the King Khalid University Hospital in Riyadh. Only Arab patients were studied. Clinical conclusions about the nature of a cardiac abnormality were always confirmed with echocardiography. In patients with active arthritis other possible articular diseases such as rheumatoid arthritis were excluded by careful clinical and serological evaluation.

The controls were all Saudi nationals of Arab origin. They were healthy, symptom free, unrelated volunteer medical students and staff members of the King Khalid University Hospital.

Fifty seven Arab (Saudi and non-Saudi) patients with acute rheumatic fever or chronic rheumatic valve heart disease were HLA typed and 17 who were non-Saudi Arabs were excluded from the statistical comparisons because all the controls were Saudis.

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Lymphocyte suspensions for HLA typing were prepared from freshly drawn human peripheral blood by defibrination.

A, B, and C antigens were determined by the standard two stage microlymphocytotoxicity technique.[8] Tissue typing trays covering all 1984 International Histocompatibility workshop specificities were obtained from One Lambda Inc. A minimum of at least 3–4 sera for each specificity were used. Each cell suspension was typed at least twice.

For HLA-DR antigens too we used 50 sera obtained from One Lambda Inc and covering all specificities. These had been characterised by separate sequential serological screening. We used the B cell lymphocytotoxicity method (2 h with antiserum, 1 h with rabbit complement), with enriched B lymphocyte suspensions, prepared from the peripheral lymphocytes in nylon wool columns.[9]

We compared the frequency of the different HLA antigens in patients with acute rheumatic fever and chronic rheumatic heart disease as a whole and the controls. We also separately compared the individual groups—that is those with rheumatic fever and chronic rheumatic heart disease with the controls and with the other disease group. The χ^2 test was used for these comparisons and significance levels were corrected for the number of sites tested.

Results

We studied 16 male and 24 female Saudi patients (mean age 21·4 years, range 13 to 53 years). Twenty five had chronic rheumatic valvar heart disease and 15 had acute rheumatic fever without evidence of chronic valvar heart disease. We also studied 17 non-Saudi Arabs (nine males and eight females; mean age 28 years, range 12–48 years).

The frequencies of the A or B antigens were not significantly different in the patients as a whole and the controls (table 1).

Of the HLA-DR antigens, only DR4 was significantly different in the Saudi population as a whole and the controls—65% in patients *vs* 12% in controls, $p < 0·01$ after correction for the 10 antigens tested, relative risk[10] 13·6 with 95% confidence interval of 10·5 to 16·7 (table 1). HLA-DR4 was also more common in patients with chronic rheumatic valvar heart disease (72% (18/25)) than in the controls ($p < 0·01$) and in those with acute rheumatic fever without chronic valvar heart disease (53% (7/14)) ($p < 0·01$). Eighteen of the 26 patients with HLA-DR4 had valvar heart disease while only seven of the 14 without HLA-DR4 had valvar heart disease (table 2).

Although HLA-DR4 was more common in patients with rheumatic heart disease (72% (18/25)) than in those with acute rheumatic fever without evidence of chronic valvular disease (53% (7/14)) this trend was not statistically significant. The frequency of HLA-DR4 was particularly high among the two most common chronic valvar abnormalities that we saw—that is mitral stenosis (83% (10/12)) and aortic incompetence (70% (7/10)).

The frequency of HLA-DR4 among the 17 non-Saudi Arabs with acute rheumatic fever or chronic rheumatic valvar heart disease was identical to that in the group of Saudi patients (65% (11/17)).

Table 1 *Frequency of HLA antigens in Saudi patients with acute rheumatic fever or chronic rheumatic heart disease and in Saudi controls*

HLA-A	*C(%) n=100*	*Pt% n=40*	*HLA-B*	*C(%) n=100*	*Pt% n=40*	*HLA-C*	*C(%) n=100*	*Pt% n=40*	*HLA-DR*	*C(%) n=100*	*Pt% n=40*
A1	25	25	B5	26	33	Cw1	11	0	DR1	28	15
A2	47	40	B7	15	18	Cw2	9	25	DR2	34	45
A3	10	20	B8	15	10	Cw3	8	10	DR3	38	18
A9	28	38	B12	9	18	Cw4	31	20	DR4	12	65*
A10	10	18	B13	2	8	Cw5	6	3	DR5	15	10
A11	10	10	B14	8	10	Cw6	11	13	DRw6	11	3
A19	36	25	B15	9	0	Cw7	29	10	DR7	28	25
A28	18	18	B16	7	0				DRw8	6	0
A29	0	3	B17	13	13				DRw9	1	0
A34	3	0	B18	8	0				DRw10	3	0
			B21	21	30						
			Bw22	2	0						
			B27	2	3						
			B35	33	13						
			B40	4	8						
			Bw41	10	8						
			Bw42	1	0						
			Bw46	0	0						

*$p < 0·01$ compared with controls.
C, controls (Saudis only); Pt, patients.

Table 2 *Comparison of frequency of HLA-DR4 in Saudi patients with or without valvar heart disease*

	DR4 +ve	*DR4 −ve*	*Total*
Chronic rheumatic valvar heart disease	18 (72%)	7 (28%)	25 (100%)
Acute rheumatic fever with no valvar heart disease	8 (53%)	7 (47%)	15 (100%)
Total	26	14	40

Discussion

Because all our patients had both mitral and aortic valve disease we feel confident that patients with valve disease with other aetiologies, such as mitral valve prolapse, were not included in our study. A past history of rheumatic fever in all our patients further strengthens this confidence.

Our results suggest that HLA-DR4 predisposes individuals to both acute rheumatic fever and chronic rheumatic valvar heart disease. These results complement the findings of two recent studies reported after we had started this study. Ayoub found HLA-DR4 in eight out of 10 white American patients with rheumatic fever.[11] Patarroyo found an alloantigen designated 883 in 66% of his patients with rheumatic fever.[12] Indirect evidence suggested that this undefined 883 antigen may be associated with the DR locus.[12]

Our results, however, are in conflict with the findings of Jhinghan *et al* from India who reported no association with HLA-DR4 but an association with HLA-DR3 in their patients with "rheumatic heart disease".[13] Whereas our patients had carefully documented evidence for a diagnosis of rheumatic fever or rheumatic heart disease no inclusion criteria were mentioned for the Indian patients. Also only 78 of these 132 Indian patients gave a past history of rheumatic fever and the positive association with HLA-DR3 was found almost entirely in the 56 patients without any past history that was suggestive of rheumatic fever. It is therefore possible that Jhinghan *et al*[13] studied a heterogenous group of patients with heart disease in which rheumatic fever was only one of many aetiologies. Alternatively, this conflict in results may reflect a true racial variation in the predisposition to rheumatic fever. Ayoub found that the high frequency of HLA-DR4 that he found in white patients was not present in the small group of black American patients.[11] The almost identical HLA-DR4 frequency that we report in both Saudi and non-Saudi Arabs suggests that this distribution at least holds good for all Arabs.

HLA-DR4 is significantly more common in patients with rheumatoid arthritis.[14] Our finding of an additional association with rheumatic fever and rheumatic heart disease suggests that HLA-DR4 positive individuals are susceptible to developing autoimmune diseases of connective tissue. This is the tissue common to both the joints and the cardiac valves—the structures that are affected in rheumatic fever, rheumatic heart diseases, and rheumatoid arthritis. This suggestion also complements the finding that HLA-DR4 positive individuals show a heightened responsiveness to collagen.[15]

It is probable that this abnormal immunological response directed against connective tissue may be initiated by many factors, in the case of rheumatic fever *Streptococcus pyogenes*. HLA-DR4 has been shown to be significantly more common in patients with post-streptococcal glomerulonephritis,[16] suggesting that heightened responsiveness to streptococci was another factor predisposing HLA-DR4 positive individuals to rheumatic fever and rheumatic heart disease. Recently, a heightened responsiveness to *Myobacterium tuberculosis* has also been reported in HLA-DR4 positive individuals.[17]

We hope to confirm our results by extending the study to families of individuals affected by rheumatic fever and rheumatic heart disease.

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References

1 Cheadle WB. Harveian lectures on the various manifestations as exemplified in childhood and early life. *Lancet* 1889;i:821–71,921.
2 Caughey DE, Douglas R, Wilson W, Hassal I. HLA antigens in Europeans and Maoris with rheumatic fever and rheumatic heart disease. *J Rheumatol* 1975;2:319–22.
3 Falk JA, Fleichman JL, Brinskie JB, Falk RE. A study of HLA antigen phenotypes in rheumatic fever and rheumatic heart disease patients. *Tissue Antigens* 1973;3:173–8.
4 Tiwari JL, Terasaki PI. Cardiovascular diseases. In. Tiwari JL, Terasaki PI, eds. *HLA and disease associations*. New York: Springer Verlag, 1985:352–62.
5 Tiwari JL, Terasaki PI. Overview, rheumatology and

joint diseases. In: Tiwari JL, Terasaki PI, eds. *HLA and disease associations*. New York: Springer Verlag, 1985:32–111.

6 Jones TD. Diagnosis of rheumatic fever. *JAMA* 1944;**126**:481.

7 Ronkotein DE, Bauer W, Dofran A. Jones criteria (modified) for guidance of rheumatic fever. *Circulation* 1956;**13**:617–20.

8 Terasaki PI, McClelland JD. Microdroplet assay of human serum cytotoxins. *Nature* 1964;**204**: 998–1000.

9 Danilous J, Terasaki PI, Park MS, Ayoub GB. B Lymphocyte isolation by thrombin-nylon wool. In: Terasaki PL, ed. *Histocompatibility testing*. Los Angeles: UCLA Tissue Typing Laboratory, 1980:287–8.

10 Svejaard A, Platz P, Ryder LO, Staub Wilson L, Thompson M. HLA and disease associations: a survey. *Transplant Rev* 1975;**22**:3–43.

11 Ayoub EM. The search for genetic determinants of susceptibility to rheumatic fever: the missing link. *Circulation* 1984;**69**:197–201.

12 Patarroyo ME, Winchester RJ, Vejerano A, *et al.* Associations of a B cells alloantigen with susceptibility to rheumatic fever. *Nature* 1979;**278**:173–4.

13 Jhinghan B, Mehra NK, Randy KS, Taneja MC, Bhatia ML. HLA blood groups, and secretor status in patients with established rheumatic fever and rheumatic heart disease. *Tissue Antigens* 1986;**27**:172–8.

14 Panayi GS, Wooley P, Bachelor JR. Genetic basis of rheumatoid disease, HLA antigens, disease manifestations, and toxic reactions to drugs. *Br Med J* 1978;**ii**:1326–8.

15 Solingar AM, Bhatnager R, Stobo JD. Cellular molecular and genetic characteristics of T cells reactivity to collagen in man. *Proc Natl Acad Sci USA* 1981;**78**:3877–8.

16 Layrisse Z, Rodriguez I, Garcia Ramirez R, Rodriguez A, Tiwari J. Family studies in HLA system in acute streptococcal glomerulonephritis. *Immunology* 1983;**7**:177–85.

17 Ottenhoff THM, Torres P, de las Aguas JT, *et al.* Evidence for an HLA-DR4-associated immune response gene for *mycobacterium tuberculosis:* a clue to the pathogenesis of rheumatoid arthritis? *Lancet* 1986;**ii**: 310–2.

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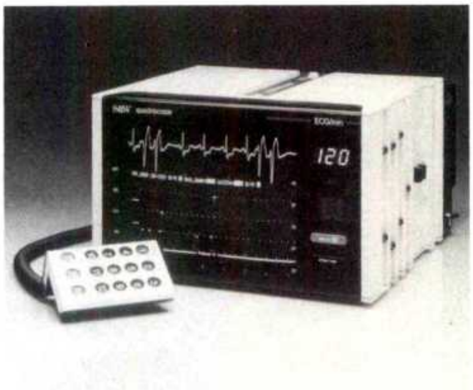

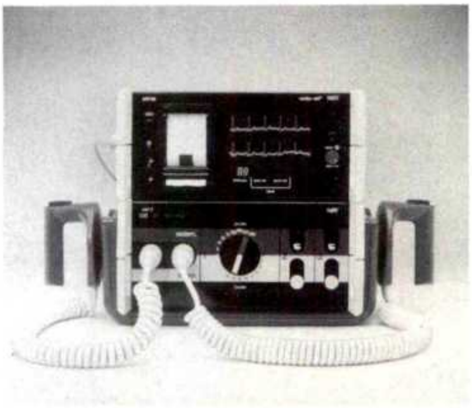

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Combined pericarditis and pneumonia caused by *Legionella* infection

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SUMMARY During a one year period acute pericarditis was diagnosed in 16 consecutive patients without acute infarction or malignancy. In two of these patients with both pericarditis and pneumonia *Legionella* infection was present. One case was caused by *Legionella longbeachae* and the other by both *Legionella longbeachae* and *Legionella jordanis*. When pericarditis is associated with pneumonia *Legionella* infection should be sought so that effective treatment with erythromycin may be started early.

Pneumonia caused by *Legionella pneumophila* has been recognised since 1976.[1] *Legionella* infection may range from a mild fever with seroconversion to the manifest Legionnaires' disease with severe pneumonia, sepsis, and several extrapulmonary manifestations,[2 3] including both myocarditis[4] and pericarditis.[5-7]

We describe two cases of severe exudative pericarditis in patients with pneumonia caused by *Legionella* infection and we emphasise the importance of separating the *Legionella* pericarditis from other causes of acute pericarditis so that treatment with erythromycin can be started early. The two cases were found among 16 pericarditis patients admitted to our hospital in the past year without acute myocardial infarction or malignant disease.

Case reports

PATIENT A

A 61 year old man, who had been in good health, was admitted with fever, non-productive cough, and headache. On admission his temperature was 40·0°C. The pulse was regular (84 beats/min) and the blood pressure was 150/80 mm Hg. A pericardial friction rub was heard. There were no signs of right ventricular failure. Repeated chest *x* ray showed diffuse fine shadowing of the left lower pulmonary lobe and small bilateral pleural effusions. The contour of the heart was normal. Cross sectional echocardiography showed a pericardial effusion with an echo free zone measuring 12 mm in diameter.

The leucocyte count was 12·9 × 10^9/l with 71% neutrophils. After blood had been taken for culture he was put on intravenous penicillin (2 million units four times a day) and netilmicin (150 mg three times a day) without effect. Because a weak positive *Legionella* titre was detected the antibiotic treatment was changed to intravenous erythromycin (1 g four times a day). Four days later oral rifampicin (300 mg three times a day) was added because a low grade fever persisted. The patient improved and his temperature became normal. Nineteen days after admission the chest *x* ray was normal and echocardiography showed only a minor pericardial effusion.

Blood cultures showed no bacterial growth. *Legionella longbeachae* titres were 32 on day 2, 2,000 on day 14, 512 on day 45, and 256 on day 73.

PATIENT B

A 44 year old previously healthy man was admitted with acute chest pain. On admission the temperature was normal, blood pressure 110/80 mm Hg, and the pulse rate was 60 beats/min. A pericardial friction rub was heard. No signs of right ventricular failure was seen. Electrocardiography showed minor ST segment elevations suggesting acute pericarditis. Chest *x* ray revealed cardiac enlargement but no lung shadows. The patient was discharged after a few days without symptoms and without audible friction rub. The cause of the pericarditis was not

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sought. Six months later he was readmitted with identical chest discomfort without fever. Again a pericardial friction rub was heard. White blood cell counts were $13 \cdot 4 \times 10^9/l$ and the erythrocyte sedimentation rate was 36 mm/h. The chest *x* ray was unchanged without signs of pneumonia. Cross sectional echocardiography revealed a pericardial effusion with an echo free zone measuring 5 mm anteriorly and 10 mm posteriorly.

Two weeks later, echocardiography showed that the size of the pericardial effusion had increased considerably and in addition paradoxical movement of the interventricular septum was seen. A pericardial fenestration improved the condition considerably. Sixteen days after the fenestration the patient again had left-sided chest pain and his temperature rose to 38·5°C. The chest *x* ray now showed an infiltrate in the left lower pulmonary lobe and a left pleural effusion. Pulmonary embolism was ruled out. The white blood cell count was $10 \cdot 8 \times 10^9/l$ with 76% neutrophils. Treatment with intravenous ampicillin (1 g four times a day) had no effect on fever while oral pivampicillin (700 mg four times a day) reduced his temperature to normal. Culture of blood and pleural fluid showed no bacterial growth. *Yersinia*, *Mycoplasma pneumoniae*, cytomegalovirus, influenza virus, *adeno* virus, and HIV infection were not found. On day 32 *Legionella* titres were: *L longbeachae* 256 and *L jordanis* 256 and on day 40: *L longbeachae* 256 and *L jordanis* 512.

He was discharged on day 47 free of symptoms, with a normal temperature, a normal white blood cell count, and a normal erythrocyte sedimentation rate. He was not treated with erythromycin during the course of the illness.

Discussion

Legionella infection is a rare cause of acute pericarditis. In 16 patients with acute pericarditis admitted within the past year we found two cases in patients with associated pneumonia and serological signs of *Legionella* infection with *L longbeachae* and *L jordanis*. Unlike *L pneumophila*, these species have not previously been associated with cardiac disease in *Legionella* infection.

Unfortunately the pericardial fluid from case B was not tested for *Legionella*; however, Maycock *et al* cultured *Legionella* from the pericardial fluid[7] and confirmed that pericarditis in their case was of a primary bacteriological origin.

Three of the four previously described cases of *Legionella* pericarditis had a fever with a temperature of less than 39·0°C.[5 6 8] Two had pericardial tamponade.[5 7] One of our cases (A) had high grade fever whereas the temperature was normal in the other case. Both our cases had pulmonary shadowing and pleural effusions. Case B had antibody titres consistent with *Legionella* infection at the time of the acute episodes of pericarditis. The pattern of the Legionella titres does not suggest that the patient caught the infection at the time of fenestration when pulmonary infiltrates were present at an early stage of the disease.

Legionella pericarditis should be suspected in cases of combined pericarditis and pneumonia. Prompt identification of *Legionella* will permit early appropriate treatment with erythromycin and this may prevent the development of long standing disease that was seen in our patients.

References

1 Fraser DW, Tsai TR, Orenstein W, *et al*. Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med* 1977;297:1189–97.

2 Tsai TF, Finn OR, Plikaytis BD, McCauley W, Martin SM, Fraser DW. Legionnaires' disease: clinical features of the epidemic in Philadelphia. *Ann Intern Med* 1979;90:509–17.

3 Swartz MN. Clinical aspects of Legionnaires' disease. *Ann Intern Med* 1979;90:492–5.

4 Gross D, Willens H, Zeldis SM. Myocarditis in Legionnaires' disease. *Chest* 1981;79:232–4.

5 Harris LF. Legionnaires' disease associated with massive pericardial effusion [Letter]. *Arch Intern Med* 1981;141:1385.

6 Landes BW, Pogson W, Beauchamp GD, Skillman RK, Brewer JH. Pericarditis in a patient with Legionnaires' disease. *Arch Intern Med* 1982;142: 1234–5.

7 Mayock R, Skale B, Kohler RB. *Legionella pneumophila* pericarditis proved by culture of pericardial fluid. *Am J Med* 1983;75:534–6.

8 Friedland L, Snydman DR, Weingarden AS, Hedges TR, Brown R, Busky M. Ocular and pericardial involvement in Legionnaires' disease. *Am J Med* 1984;77:1105–7.

Br Heart J 1987;58:665–8

Case reports

A case of left atrial haemangioma: echocardiographic, surgical, and morphological features

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SUMMARY A slow growing encapsulated haemangioma of the left atrium was diagnosed by means of cross sectional echocardiography. The heterogenous nature of the tumour was reflected in a central area of relative echolucency. After successful surgical removal of the tumour, the patient's symptoms of lethargy and limited exercise capacity improved considerably.

Case report

A sixty three year old woman presented with a fourteen year history of fatigue and shortness of breath. When she was first seen a late systolic murmur had been noted and a diagnosis of mitral regurgitation was made. During follow up the signs remained largely unchanged apart from the development of atrial fibrillation which was treated with digoxin. Her symptoms of fatigue and breathlessness gradually became worse, however, and the murmur was noted to have become louder and longer. Because of progressive enlargement of the cardiac silhouette on chest *x*-ray she was admitted to hospital for further investigation.

On admission she reported breathlessness after walking 100 yards on the flat. She had noticed palpitation, especially on change of posture. Physical examination showed that she was in controlled atrial fibrillation with pronounced right and left parasternal impulses. On auscultation there was a loud first sound and a normally split second sound; a late systolic murmur which varied markedly with posture, was loudest at the apex, and radiated to the axilla. There were no stigmata of bacterial endocarditis or signs of heart failure.

Full blood count was normal; 3% reticulocytes were found. The erythrocyte sedimentation rate was 48 mm/h. On chest *x* ray the left atrium seemed to be enlarged. The electrocardiogram showed atrial fibrillation and widespread non-specific T wave changes.

An exercise test was terminated at the end of stage 2 of the modified Bruce protocol because of considerable breathlessness and ventricular bigeminy.

At cardiac catheterisation pressures (mm Hg) were as follows: pulmonary capillary wedge, V = 25, mean 12; pulmonary artery, 35/15; right ventricle, 35/8; right atrium, mean 7; aorta, 160/60; left ventricle, 160/12. There were no aortic or mitral valve gradients.

It was noted that the right heart catheter was displaced to the right as it traversed the right atrium.

Coronary angiography showed a normal myocardial circulation from the right and left coronary systems but injections from both the right and left showed an abnormal circulation in the region of the atria.

Cross sectional echocardiography showed a mass 4 × 6 cm in the region of the interatrial septum. The mass was immobile and multiple echolucent areas suggested a "soft" or cystic centre (fig 1). In view of these findings it was felt that the left atrium should be surgically explored.

At operation we found a spongy lobulated mass 15 cm × 10 cm arising from the epicardial surface of

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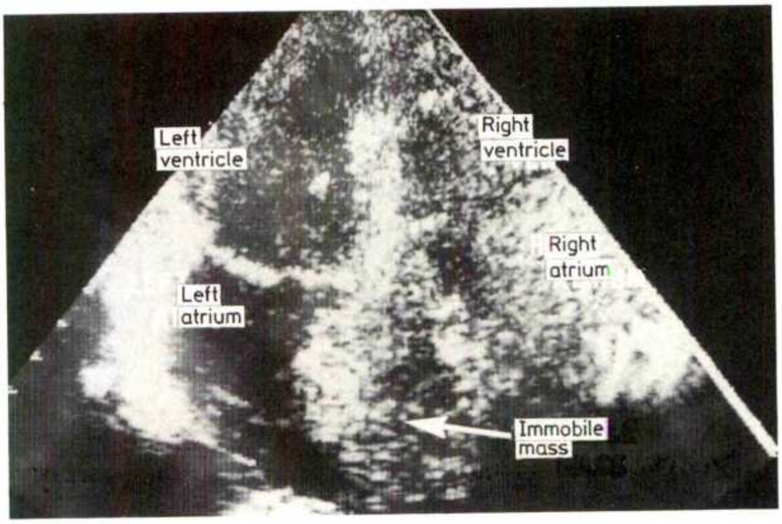

Fig 1 *Four chamber cross sectional echocardiogram showing tumour mass in region of interatrial septum.*

the posterior wall of the left atrium close to the orifices of the superior pulmonary veins and tracking anteriorly from the transverse sinus medial to the superior vena cava. An additional separate mass (2 cm × 2 cm × 1 cm) of the same consistency arose from the anterior surface of the aortic root and extended into the atrioventricular groove.

The left atrium was explored on cardiopulmonary bypass. It was found that the tumour had not arisen from within the atrium but rather had been compressing it from without. The mitral valve showed slight prolapse but this was not considered to be sufficiently severe to warrant repair. The visceral pericardium which was encapsulating the tumour was incised and the haemangioma was enucleated with some difficulty. The patient made an uneventful recovery and her symptoms of fatigue and limited exercise capacity improved considerably. She remains well five years after operation.

HISTOLOGY

Macroscopically the excised mass measured 14 cm × 10 cm × 4·5 cm and was spongy in consistency (fig 2). It was divided into ill-defined lobules by fibrous septa and these lobules were composed of a meshwork of small blood-filled spaces. There was a more centrally placed yellow firmer area measuring 8 cm × 3 cm situated towards one end of the specimen.

Light microscopy showed a benign haemangioma of the atrium. The predominantly spongy areas of the tumour were composed of large vascular spaces lined by flattened endothelium and in some areas these contained elastic and other collagen fibres in their walls. The more solid yellow area was made up of loose myxoid tissue containing small vessels.

The separate specimen removed from the aortic root had a similar histological appearance as the main tumour mass.

Discussion

Primary tumours of the heart are rare—according to McAllister and Fenoglio in 1978 there were fewer than 1000 published reports of cases of cysts and neoplasms of the heart and pericardium.[1] The analysis of 533 of their own cases by these workers showed that 76% were benign and that the commonest tumour was a myxoma, accounting for 25% of all such lesions of the heart and pericardium. A haemangioma is the commonest vascular tumour arising from the heart but accounts for only approximately 5% of all benign cardiac tumours in adults.[1 2]

In 1975 Tabry *et al*, reporting a case similar to our own, found only 35 cases of haemangioma of the heart reported throughout the world.[3] Since these reports, we have found only one further case—a right ventricular haemangioma in a fifteen year old girl.[4] This last case showed cross sectional echocardiographic features similar to those of our patient but the tumour was found to be inoperable.

Three out of fifteen cases reported by McAllister and Fenoglio presented with symptoms similar to those occurring with myxomas and at necropsy had

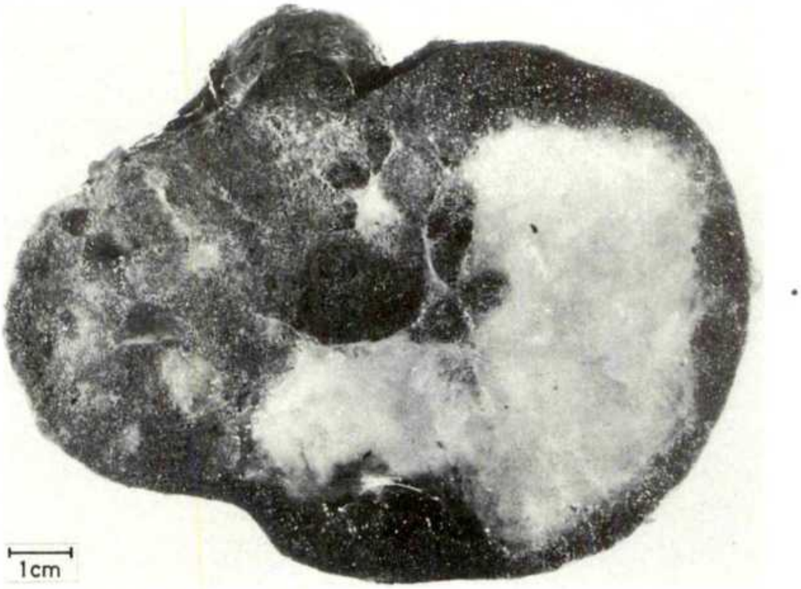

Fig 2 *Cut surface of surgically excised tumour showing ill-defined lobules and distinct central myxoid area.*

a tumour protruding into a cardiac chamber— the right atrium in two cases and the left ventricle in a third. In two a mass was discovered on routine chest *x* ray and they were operated on with a suspected diagnosis of pericardial cyst. Histologically, haemangiomas of the heart are identical with haemangiomas occurring at other sites in the body. They may consist of closely packed capillary structures or widely dilated vascular channels lined by flattened endothelial cells and with focal connective tissue in the walls— the pattern of cavernous haemangioma—as seen in the present case.

Cardiac tumours are rare, but the commonest, myxomas, can be diagnosed because their intrinsically mobile nature aids in their detection by echocardiography. By contrast, haemangiomata, which are much less common, are sessile. This explains why in the present case M mode echocardiography could not distinguish the haemangioma from an artefact. Cross sectional study showed a mass 4 cm × 6 cm in the region of the interatrial septum. A striking feature was the lack of homogeneity of the reflected ultrasound from the mass which had an apparently echolucent centre. Morphologically these findings were found to correspond with a large area in which the dense sinusoidal tumour had apparently undergone spontaneous degeneration leaving a loose stroma. Similar structural and echocardiographic features have been previously described[4] and may represent a means of recognising such tumours on ultrasound.

In our patient, radiological evidence suggested that the tumour had grown slowly and progressively over a period of ten years. It was completely encapsulated, in contrast with the typical friable, gelatinous composition of myxomas. There had been no clinical evidence to suggest embolism seen with unencapsulated tumours in the left atrium.

There was no evidence of major haemodynamic disturbance in our patient. A late systolic murmur was consistently noted over the years. We found that the intensity of this murmur varied strikingly with posture, being much louder when the patient was upright. In addition, a formal exercise test was terminated in stage 2 of the Bruce protocol because of ventricular bigeminy. These features suggest that the tumour may have affected cardiac function in the upright position by impairing left atrial emptying. Postoperatively there was a great subjective improvement in her exercise tolerance and she reached the end of stage 4 of the Bruce protocol.

Intra-atrial masses derive a blood supply from the coronary circulation. Long standing left atrial thrombosis in patients with rheumatic mitral disease may be revealed as a "blush", especially from the left coronary injection. Myxomas too have a vascular supply from the coronary arteries.[5 6] The appearance of the coronary angiogram of our patient showed the sinusoids of the haemangioma filling at the same time as the coronary venous phase.

We thank Dr P A Revell for his help.

References

1 McAllister HA, Fenoglio JJ. *Tumors of the cardiovascular system. Atlas of tumor pathology; Fasicle 15, Second Series.* Washington DC: Armed Forces Institute of Pathology, 1978.

2 Silverman NA. Primary cardiac tumours. *Ann Surg* 1980;**191**:127–38.

3 Tabry IF, Nassar VH, Rizk G, Touma A, Dagher IK. Cavernous haemangioma of the heart: case report and review of the literature. *J Thorac Cardiovasc Surg* 1975;**69**:415–20.

4 Ryan TJ, Aretz TH. A fifteen-year-old girl with a right ventricular mass. *N Engl J Med* 1983;**308**:206–14.

5 Marshall WH, Steiner RM, Wexler L. "Tumour vascularity" in left atrial myxoma, demonstrated by selective coronary arteriography. *Radiology* 1969;**93**:815–6.

6 Berman ND, McLaughlin PR, Bigelow WG, Morch JE. Angiographic demonstration of blood supply of right atrial myxoma. *Br Heart J* 1976;**38**:764–6.

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Left atrial vascularised thrombus diagnosed by transoesophageal cross sectional echocardiography

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SUMMARY This report describes a patient with a Björk-Shiley mitral valve prosthesis in whom transoesophageal cross sectional echocardiography revealed a large vascularised mass within the left atrial appendage with smoke-like opacification of blood flow in the left atrium. Transoesophageal cross sectional echocardiography gave a detailed image of the lesion which was unobtainable with precordial cross sectional echocardiography.

Left atrial thrombi are common in patients with low cardiac output and are predominantly situated in the left atrial appendage.[1] Precordial cross sectional echocardiography is the technique of choice for the identification of intracardiac mass lesions. However, the left atrial appendage is difficult to visualise and morphological details are rarely obtained.[2] Transoesophageal echocardiography offers the potential of imaging this cardiac area in detail.[3 4]

We describe the role of transoesophageal cross sectional echocardiography in the detailed analysis of a left atrial vascularised thrombus.

Case report

A 66 year old woman was admitted with congestive cardiac failure and central cyanosis. In 1976 the mitral valve had been replaced with a spherical 25 Björk-Shiley prosthetic valve because of severe mitral valve stenosis and moderate regurgitation. She had had atrial fibrillation for many years. Five months before admission a VVI pacemaker was implanted because long periods of asystole and rapid paroxysmal atrial fibrillation were causing symptoms. Three weeks before admission she had noticed increasing fatigue and general malaise. On admission she was in New York Heart Association functional class IV and was taking digoxin, diuretics, and oral anticoagulants.

On physical examination she had orthopnoea and was afebrile. The blood pressure was 170/60 mm Hg and the pulse rate 90 beats/minute. Jugular venous pressure was elevated. A strong right ventricular lift was palpated at the left sternal border. A loud pulmonary closure sound was heard. The prosthesis produced crisp metallic opening and closing clicks. There was no mitral imcompetence but there was a grade III/VI tricuspid murmur. The liver was enlarged 5 cm below the costal margin. There was no peripheral oedema. There were no physical signs of endocarditis or of peripheral embolisation. The electrocardiogram showed atrial fibrillation and right ventricular hypertrophy. The cardiothoracic ratio on the chest *x* ray was 0·66 and there were signs of pulmonary congestion.

While she was on oxygen support arterial blood gas analysis showed severe hypercapnoea, hypoxaemia, and low oxygen and carbon dioxide saturations. Routine laboratory investigations were within normal limits. There were no signs of haemolysis. Emergency right heart heart catheterisation showed pulmonary hypertension (64/24 mm Hg), a raised pulmonary capillary wedge pressure (27 mm Hg) and mean right atrial pressure (12 mm Hg), and a low cardiac index (2·6 l/min/m^2).

Precordial cross sectional echocardiography with a 3·5 MHz transducer showed left atrial dilatation with a left atrial dimension of 100 mm; the left ventricle was of normal size with good contractility. Continuous wave Doppler investigation showed an early diastolic velocity of 2·3 m/s over the prosthesis and a mean velocity of 1·8 m/s. She improved dramatically on intravenous vasodilators, diuretics, and oxygen. Repeat catheterisation after two weeks showed that right and left cardiac pressures had dropped to normal. The cardiac index was

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1·8 l/min/m². There was no mitral valve incompetence. No gradient was found over the mitral prosthesis and at screening disc motion seemed unimpaired. There was grade 2 aortic incompetence. The coronary arteries appeared normal. Cineangiography showed that the atrial branch of the left coronary artery supplied a mass lesion within the left atrium (fig 1) but gave no specific details about the mass. A repeat continuous wave Doppler study showed that the mean velocity over the valve prosthesis had dropped to 1·1 m/s.

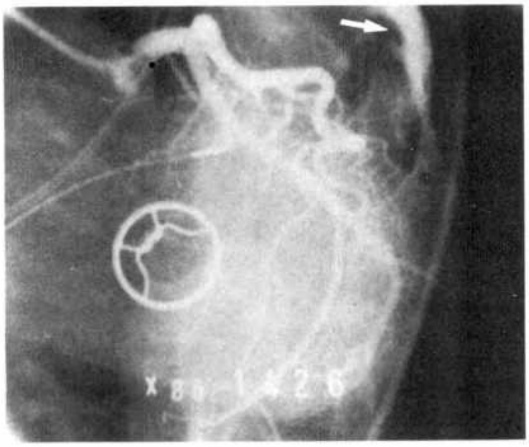

Fig 1 *Left coronary artery angiogram showing a vascularised structure in the left atrium (arrow).*

Because precordial echocardiography gave an image of unsatisfactory quality, we decided to use transoesophageal echocardiography to obtain more details about the nature, extent, and location of the mass. We used a 5·6 MHz transducer (64 elements) mounted on an Olympic gastroscope and interfaced with a commercially available ultrasonograph.[4] The inter-element spacing of the individual elements is 210 μm, so that the active area of the transducer resembles the active area of precordial 5 MHz phased array transducers. The housing of the oesophageal transducer is much smaller than that of the precordial transducer.

The Björk-Shiley prosthesis and disc showed no apparent abnormalities and its motion was undisturbed. The enlarged left atrial cavity was completely filled with echoes swirling in phase with the inflow of blood from the pulmonary veins (fig 2). From the dilated left atrial appendage a mass emerged into the left atrial cavity along the lateral wall, reaching the orifices of the left pulmonary veins. In cross-section the lesion measured approximately 20 × 80 mm. Within this lesion there were several echo-free spaces (fig 2). The image of the

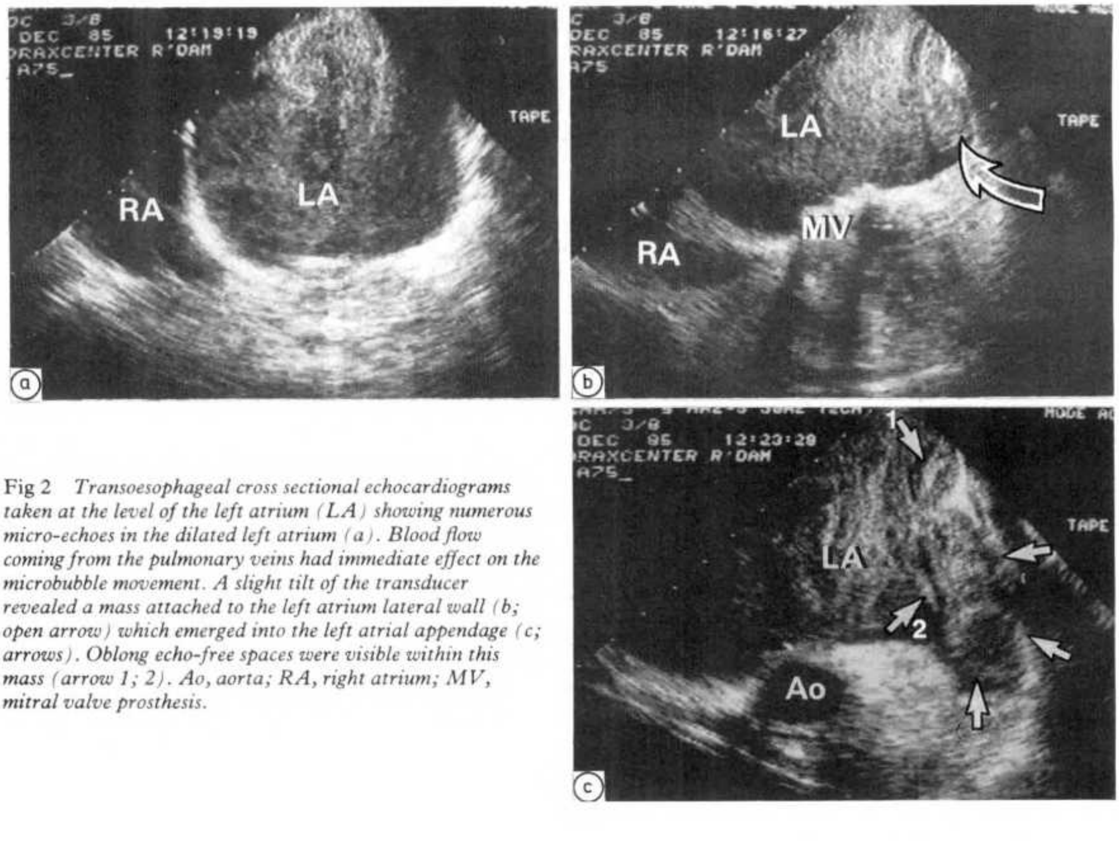

Fig 2 *Transoesophageal cross sectional echocardiograms taken at the level of the left atrium (LA) showing numerous micro-echoes in the dilated left atrium (a). Blood flow coming from the pulmonary veins had immediate effect on the microbubble movement. A slight tilt of the transducer revealed a mass attached to the left atrium lateral wall (b; open arrow) which emerged into the left atrial appendage (c; arrows). Oblong echo-free spaces were visible within this mass (arrow 1; 2). Ao, aorta; RA, right atrium; MV, mitral valve prosthesis.*

mass suggested a thrombus. The favourable clinical course and improvement of the non-invasive and invasive data suggested that the patient's condition was the result of intermittent valve obstruction produced by dislodged thrombus. We therefore decided to operate. We found a large organised thrombotic mass attached to the atrial lateral wall and partially obstructing the entrance of the left pulmonary veins. The patient's postoperative course was uneventful. Microscopy showed typical thrombus material with fibrin layers and scar tissue containing small and medium-sized vessels. The left atrial endocardium consisted of elastic fibres mixed with scar tissue, and the myocardium was collagenous with scattered elastic tissue.

Discussion

Echocardiographic imaging of circulating blood in the left atrium has been described in obstructive mitral valve disease.[5,6] The low shear rates associated with low blood flow favour rouleaux formation,[7,8] and predispose to thrombus formation.[6] Our patient had scattered echoes from the atrial blood pool and an abnormal mass in the left atrium. Doppler, cardiac catheterisation studies, and surgical inspection showed no evidence of mitral valve obstruction. The possible presence of concomitant aortic regurgitation was obscured by the diastolic inflow Doppler signal over the mitral valve prosthesis. We assume that the echogenicity of the atrial blood was caused by the low blood flow created by the aneurysmal left atrial dilatation that in turn was the result of longstanding mitral valve disease before valve replacement and by low cardiac output. This might have been the result of the partial loss of atrial muscular fibres that was confirmed at postoperative microscopic investigation. This resulted in progressive left atrial enlargement and impaired atrial function. In 1955 Bailey described a similar condition of the right atrium.[9]

Because attenuation along the ultrasound propagation path is much reduced by transoesophageal echocardiography a high frequency transducer can be used. High frequency improves resolution and also increases the sensitivity for back-scattering. In particular small particles will produce a back-scattering signal with an intensity (I) which shows a strong non-linear relation with frequency (f), where $I \div f^4$.[10] Thus the sensitivity for objects producing back-scattering will increase with frequency.

Under normal conditions increased back-scattering in blood at diagnostic frequencies (2–5 MHz) can only be explained by an increase in the ratio of blood particle size to wavelength. The mechanism for this increase in particle size must be an aggregation of blood cells associated with low blood flow. A high frequency transoesophageal transducer will therefore detect stagnant blood flow more effectively than precordial examinations at lower frequencies.[11] There are two possible explanations why precordial echocardiography failed to image the lesion. Firstly the position of the oesophageal transducer results in a much better signal to noise ratio than the precordial position. Also the position of the thrombus in relation to the precordial acoustic window may hamper adequate imaging. The high resolution images also showed oblong echolucent areas within the lesion that indicate the vascularisation of this lesion, which was also noted on the angiograms.

We thank Dr Max Haalebos, who performed cardiac surgery; Dr Nienke Essed, for pathological and anatomical studies; and Kees Ligtvoet, who gave technical advice.

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References

1 Wallach JB, Borgatta EF. *Rheumatic heart disease*. Springfield, Illinois: Charles C Thomas, 1962.

2 Herzog CA, Bass D, Kane M, Asinger R. Two-dimensional echocardiographic imaging of left atrial appendage thrombi. *J Am Coll Cardiol* 1984;**3**:1340–4.

3 Aschenberg W, Schlüter M, Kremer P, Schröder E, Siglow V, Bleifeld W. Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. *J Am Coll Cardiol* 1986;**7**:163–6.

4 Gussenhoven EJ, Taams MA, Roelandt J, *et al*. Transesophageal two-dimensional echocardiography: its role in solving clinical problems. *J Am Coll Cardiol* 1986;**8**:975–9.

5 Garcia-Fernandez MA, Moreno M, Banuelos F. Two-dimensional echocardiographic identification of blood stasis in the left atrium. *Am Heart J* 1985;**109**:600–1.

6 Beppu S, Nimura Y, Sakakibara H, Nagata S, Park YD, Izumi S. Smoke-like echo in the left atrial cavity in mitral valve disease: its features and significance. *J Am Coll Cardiol* 1985;**6**:744–9.

7 Mikell FL, Asinger RW, Elsperger S, Anderson WR, Hodges M. Regional stasis of blood in the dysfunctional left ventricle: echocardiographic detection and differentiation from early thrombosis. *Circulation* 1982;**66**:755–63.

8 Sigel B, Coelho UCV, Spigos DG, *et al*. Ultrasonography of blood during stasis and coagulation. *Invest Radiol* 1981;**16**:71–6.

9 Bailey CP. *Surgery of the heart*. Philadelphia: Lea and Febiger, 1955:413.

10 Morse PM, Ingard KU. *Theoretical acoustics*. New York, Saint Louis, San Francisco, Toronto, London, Sydney: McGraw Hill, 1968:400–66.

11 Iliceto S, Papa A, Antonelli G, Sorino M, Amico A. Spontaneous contrast echocardiography. *Echocardiography* 1985;**2**:455–65.

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Combined percutaneous balloon dilatation of the aortic valve and coronary angioplasty

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SUMMARY A 75 year old man with severe angina caused by aortic stenosis and coronary artery disease was considered to be unsuitable for cardiac surgery after the recent removal of a bronchial carcinoma. Combined percutaneous balloon dilatation of the aortic valve and right coronary angioplasty considerably ameliorated the patient's angina.

Case report

A 75 year old man had a two year history of exertional angina and dyspnoea that was getting worse despite treatment with propranolol and bumetanide. Left heart catheterisation in May 1985 demonstrated an aortic valve gradient of 60 mm Hg. Coronary angiography showed a discrete 90% stenosis in the mid portion of the dominant right coronary artery (fig 1) and several areas of stenosis in the left anterior descending artery with a maximum narrowing of 90%. On admission in November 1985 for aortic valve replacement and aortocoronary bypass surgery a preoperative chest *x*-ray demonstrated a mass in the upper lobe of the right lung. Cardiac surgery was cancelled and at lobectomy a well differentiated adenocarcinoma was removed; no local spread of tumour was found. No evidence of tumour recurrence was found in the following months but the angina became progressively worse, occurring when he walked across a warm room and at rest.

In September 1986 percutaneous coronary angioplasty and balloon dilatation of the aortic valve were attempted. The heavily calcified aortic valve was approached from the brachial artery and crossed with an exchange guide wire and progressively dilated with 10, 14, and 16 mm balloons (Meditech). Each balloon was inflated three times for 20 seconds at a pressure of 3–5 atmospheres. The femoral artery pressure was recorded continuously and fell slightly during balloon inflation. The gradient was reduced to 35 mm Hg (fig 2). Aortography demonstrated no change in the minimal aortic regurgitation. A brachial guide catheter could not be positioned in the right coronary artery, so a femoral guide catheter was used. Narrowing of the right coronary artery was reduced from 90% to 30% with an ACS ultra-low profile 3·0 mm balloon. No attempt was made to dilate the diffusely diseased left coronary artery. The patient tolerated this 130 minute procedure and was discharged after three days.

One year later he has considerably improved effort tolerance. Apart from chest pain on walking up steep hills, he is free of angina.

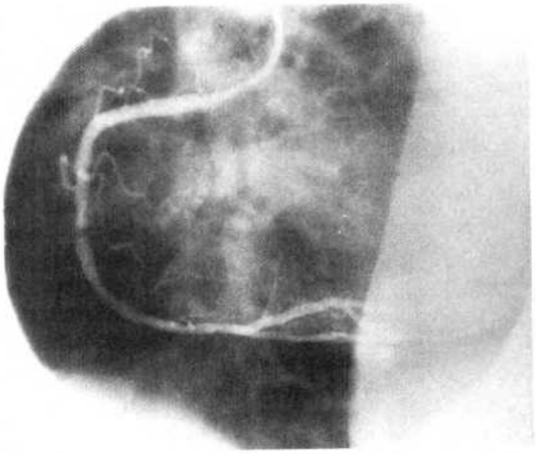

Fig 1 *Right coronary angiogram before coronary angioplasty.*

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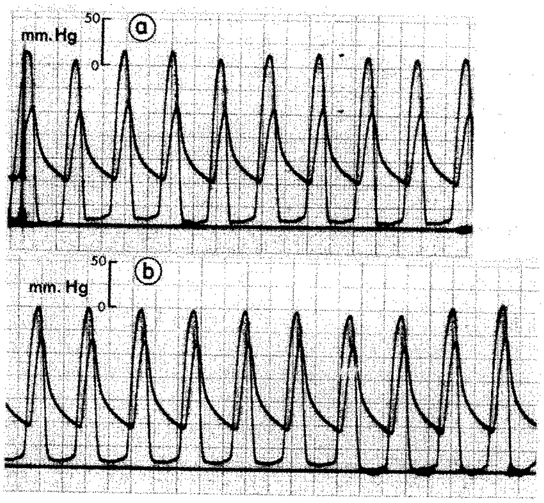

Fig 2 *Simultaneous pressure traces from the left ventricle and femoral artery (a) before and (b) after aortic valvuloplasty.*

Discussion

Angioplasty is a well established intervention that is suitable for some patients with coronary artery disease. Until recently many patients with severe aortic stenosis, for whom valve replacement was considered inappropriate, could be offered little effective treatment. Balloon dilatation of the calcified aortic valve has now been shown to be effective, though the safety and long term benefits of the procedure have yet to be established.[1 2]

Some patients with severe aortic stenosis and angina have clinically significant coronary artery disease. Our case shows that combined balloon dilatation of coronary stenosis and the aortic valve can produce worthwhile improvement in symptoms. Such palliative procedures may be appropriate in patients who are considered to be unsuitable for cardiopulmonary bypass surgery.

The duration of the combined procedure was prolonged because we could not obtain a stable position for the guide catheter in the right coronary artery from the brachial approach; but the patient remained comfortable throughout the procedure. The best sequence of balloon dilatations is uncertain. An initial coronary angioplasty would improve myocardial perfusion and might reduce the hazards of balloon dilatation of the aortic valve.[3]

References

1 Cribier A, Savin T, Saoudi N, Rocha P, Berland J, Letac B. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement. *Lancet* 1986;**i**:63–7.
2 Jackson G, Thomas S, Monaghan M, Forsyth A, Jewitt D. Inoperable aortic stenosis in the elderly: benefit from percutaneous transluminal valvuloplasty. *Br Med J* 1987;**294**:83–6.
3 Starkey I R, Cumberland D C, Oakley G D G. Balloon aortic valvuloplasty for severe calcific aortic stenosis: effective but not without hazard [Abstract]. *Br Heart J* 1987;**57**:69–70.

Br Heart J 1987;**58**:674–5

Coronary artery surgery and myxoedema

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SUMMARY A patient with a preoperative diagnosis of myxoedema had triple vessel coronary artery bypass surgery. The perioperative and postoperative course was essentially uneventful. The most appropriate management of a patient with coronary artery disease who has concomitant myxoedema is first to improve myocardial blood flow by relieving coronary obstruction and then to treat the thyroid deficiency.

Management of patients with concomitant myxoedema and coronary artery disease is difficult.[1] In 1938 Smyth described the clinical dilemmas associated with providing adequate thyroid hormone replacement therapy in such patients.[2] Thyroxine supplementation commonly increases anginal symptoms, and progression to myocardial infarction has been reported.[3] This is a particular problem when the myocardial disease is considered suitable for coronary artery revascularisation. Paine *et al* reported one death in six patients after attempted preoperative hormone replacement.[1] To date, there has not been a large study of the diagnosis and subsequent management of hypothyroid patients with chest pain. In patients with myxoedema coronary artery disease tends to be more extensive[4] than usual and these patients require detailed and careful investigation.

We present a case report which we believe lends support to a specific and useful form of management by adequate investigation followed by coronary artery revascularisation and postoperative thyroid hormone replacement therapy.

Case report

A 35 year old man was admitted to the cardiac surgery unit for myocardial revascularisation. He gave a three year history of increasing angina pectoris with recent exacerbation making him housebound. He was now experiencing rest and nocturnal pain and further questioning revealed recent weight gain (20 lb (10 kg)) and cold intolerance. Angiography, a year before, had demonstrated severe triple vessel disease with $\geqslant 70\%$ stenosis of the marginal circumflex and left anterior descending coronary arteries, complete blockage of the right coronary artery, and moderate distal disease.

He was obese (weight 14 st 4 lb (90 kg), height 5 ft 10 in (178 cm)). The pulse rate was 80 beats per minute and regular. His blood pressure was 100/60 mm Hg prone, and heart sounds were normal. The jugular venous pressure was not elevated, there was no peripheral oedema, and his chest was clear. He had normal distribution of body hair and no palpable masses in neck or abdomen. Neurological examination suggested sustained ankle jerks.

Routine preoperative investigations were performed: haemoglobin (14·6 g/dl); mean corpuscular volume (120 fl (normal range 84–98)); normal platelet and leucocyte counts. Although creatine kinase was raised (100 U/l (normal range 30–140 U/l)), the concentration of the isoenzyme creatine kinase was within normal limits. The electrocardiogram showed low voltages with widespread T wave flattening and minimal ST depression in chest leads V4 to V6. There were no specific changes suggestive of myocardial infarction.

We thought that the initial haematological and biochemical findings together with the clinical and electrocardiographic findings suggested a diagnosis of myxoedema. Thyroid function tests were performed. These showed a free thyroxine value of 4 pmol/l (normal range 9–26), thyroid stimulating hormone 33 mU/l (normal range 0–5). The diagnosis of myxoedema was confirmed immediately before operation. The operation was performed as planned with reverse saphenous vein grafting into the three main vessels; each graft required endarterectomy.

Although the procedure was carried out under controlled hypothermia the patient's temperature

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was 37·5°C when he came off bypass. The patient's postoperative course was essentially uneventful; however, he did require dopamine support (5 μg/kg/min in reducing dosage) for twelve hours after operation. His temperature fell to 35·3°C when he returned to the recovery ward. It remained at this level for 24 hours and was not normal until 48 hours after operation. Twenty four hours after operation, he was extubated and was started on L-thyroxine 25 μg/day; the dose was gradually increased over ten days to 100 μg/day.

He was discharged 14 days after operation and remained well and symptom free until four months after operation when anginal symptoms returned. At this stage his haemoglobin was 6·0 g/dl and mean corpuscular volume was 98 fl; serum vitamin B_{12} was at the lower limit of normal and serum folate at the upper limit of normal. Bone marrow examination revealed gross megaloblastic change at all stages of erythropoiesis. Pernicious anaemia was suspected; this diagnosis was confirmed by a positive Schilling test. Hydroxocobalamin treatment was started. After the haemoglobin concentration had returned to normal, the anginal symptoms regressed significantly but did not disappear. He continued to be biochemically and clinically euthyroid.

Discussion

In patients with severe and, in particular, unstable angina thyroid replacement therapy can exacerbate symptoms by increasing the heart rate, myocardial contractility, and myocardial oxygen consumption. Thus patients with angina and myxoedema often end up with continuing angina and inadequately treated myxoedema.[1] Coronary artery bypass surgery may provide a more rational therapeutic approach to this combination of diseases because after successful coronary revascularisation the myxoedematous patient may be better able to tolerate adequate doses of thyroid preparations.[1 3 4] We believe that our experience with the present case supports this approach.

Our patient presented with clinically unstable angina and clinical and laboratory findings suggestive of myxoedema. Angiography indicated that he was a suitable, but not ideal, candidate for a revascularisation procedure (moderate "distal disease" was demonstrated). It was clear that he was not going to be able to withstand full hormone replacement therapy because he was profoundly hypothyroid and yet had rest pain on maximal antianginal treatment. With this in mind, and in view of the potential inadequacies of the available medical management, we decided to proceed to bypass surgery.

Operation in myxoedematous patients is more hazardous because of the increased risks of infection, cardiovascular instability and collapse, respiratory depression, paralytic ileus, and of the development of an inappropriate antidiuretic hormone-like syndrome. In addition body tissue is more friable. These potential problems must be weighed against the real danger of the complications associated with medical management. Once surgery is decided upon, the question of preoperative thyroid hormone replacement therapy must be faced and the conflicting evidence analysed.

Nelson *et al* reported two patients with myxoedema who underwent coronary artery bypass surgery; one did not have thyroid hormone supplementation before operation.[4] His postoperative course was complicated by an inappropriate antidiuretic hormone-like syndrome, paralytic ileus, and infection. The second patient was given a small daily dose of 10 μg thyroxine before operation and did well after operation on a dose of 200 μg of L-thyroxine. The experience of Paine *et al,* however, suggests that thyroid replacement is not necessary before operation (only one of his series of six patients had a complicated course) and that thyroxine should be introduced gradually after operation with regular assessment of electrocardiograms and serum concentrations of thyroid stimulating hormone. Myerowitz *et al* found no noticeable improvement in haemodynamic function (cardiac index, left ventricular index, oxygen consumption) in 10 patients treated with small doses of thyroxine before operation.[3] They therefore concluded that preoperative treatment offers no clinical or haemodynamic benefit.

The result in our patient supports the view that coronary artery surgery is not contraindicated in cases of untreated myxoedema and that revascularisation can be performed safely in such cases before thyroid replacement therapy, and indeed is the regimen of choice. Mild angina has persisted in our patient although it has become more stable. Because he remains euthyroid we believe that extensive distal disease is the main reason for the persistence of angina.

References

1 Paine TD, Rodgers WJ, Baxley WA, Russell RD. Coronary artery surgery in patients with incapacitating angina pectoris and myxoedema. *Am J Cardiol* 1977;**40**:226–31.

2 Smyth CJ. Angina pectoris and myocardial infarction as complication of myxoedema with special reference to the danger of treatment with thyroid preparations. *Am Heart J* 1938;**15**:552–660.

3 Myerowitz PD, Kamienski RW, Swanson DK, Chopra PS. Diagnosis and management of the hypothyroid patient with chest pain. *J Thorac Cardiovasc Surg* 1983;**86**:57–60.

4 Nelson JC, Palmer FJ, Bowyer AF. The successful treatment of myxoedema and coronary artery disease in patients intolerant of thyroid hormone. *Med Arts Sci* 1974;**28**:15–22.

Br Heart J 1987;58:676–7

The use of an endotracheal tube for cannulation of left superior vena cava via coronary sinus for repair of a sinus venosus atrial septal defect

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SUMMARY A reinforced cuffed endotracheal tube was used to drain blood from a left superior vena cava via the coronary sinus during patch repair of a sinus venosus defect in a 65 year old patient. This approach produced good drainage and a bloodless operative field.

It is estimated that a left superior vena cava is present in approximately 0·3% of the general population[1 2] and in 4% of patients with heart disease.[3-6] Commonly it drains into the coronary sinus. If adequate cardiopulmonary bypass is to be established for intra-atrial procedures, such as closure of atrial septal defects, the left sided superior vena cava must be drained adequately. A cardiotomy suction cannula may be used to control the left superior vena caval flow through the coronary sinus.[7] Alternatively, the left superior vena cava can be cannulated directly.[8] The use of the cuffed, reinforced endotracheal tube (Mallinckrodt) not only removes more blood from the operative field than use of a cardiotomy suction cannula but also is easier and less time consuming than direct cannulation and snaring of the persistent left superior vena cava.

Case report

A 65 year old man first presented with atrial fibrillation, heart failure, and clinical signs of an atrial septal defect, which was confirmed by catheter studies. He refused operation because his symptoms improved on medical treatment. Ten years later he again presented with increasing dyspnoea; on this occasion he consented to operation. Cardiac catheter studies again confirmed an atrial septal defect and 3·6:1 left to right shunt, pulmonary hypertension, a left sided superior vena cava draining to the coronary sinus, and an absent innominate vein.

Surgical repair was performed through a median sternotomy. As expected, there was no innominate vein. A large left superior vena cava and small right superior vena cava drained with both the superior and inferior pulmonary veins into a sinus venosus abnormality which communicated with the left atrium in a conventional way through a defect high in the atrial septum. Cardiopulmonary bypass was established from snared cannulas in the right superior and inferior vena cava to the aortic root. The patient was cooled to 28°C, the aorta was cross clamped, and cardioplegia was used. A right atriotomy was made and the atrial septal defect and large coronary sinus were noted. A size 6 reinforced cuffed endotracheal tube (Mallinckrodt) was then inserted via the coronary sinus into the left superior vena cava and connected to the venous drainage pipes. We controlled blood leakage around the tube and sustained good drainage by intermittently adjusting the volume of the endotracheal tube cuff. We did not need to use snugging of the left superior vena cava or pump suckers to maintain a dry and clear operative field. Throughout the procedure venous drainage from the left superior vena cava was adequate with a small adjustment of the cuff. The cannula was removed from the coronary sinus before atriotomy repair. Cardioversion with a DC shock was used to convert ventricular fibrillation to nodal rhythm as the patient came off bypass. He required pacing for about 24 hours; after this the preoperative rhythm of atrial fibrillation resumed.

Discussion

Surgical repair of an atrial septal defect in adults and in patients over 60 years of age has been reported before.[9-11] As an isolated anomaly a left sided

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superior vena cava that drains into the coronary sinus is of no significance. However, assessment of anomalous venous drainage, such as a left superior vena cava, either preoperatively by conventional radiology, catheter studies, and echocardiography, or at operation is essential when operative repair of congenital anomalies of the heart is being undertaken. We found that cannulation of the left superior vena cava via the coronary sinus with a cuffed endotracheal tube produced adequate bypass simply and quickly and a clear field of vision. This improved the technical ease with which the atrial septal defect was closed with a patch.

References

1 Cha EM, Khoury GH. Persistent left superior vena cava. Radiologic and clinical significance. *Radiology* 1972;**103**:375–81.

2 Abrams HD, ed. *Abrams angiography: vascular and interventional radiology*. 3rd ed. Boston: Little, Brown, 1983:936.

3 Winter FS. Persistent left superior vena cava. Survey of the world literature and report of thirty additional cases. *Angiology* 1954;**5**:90–132.

4 Campbell M, Deuchar DC. The left-sided superior vena cava. *Br Heart J* 1954;**16**:423–39.

5 Gensini GG, Caldina P, Casaccio F, Blount SG. Persistent left superior vena cava. *Am J Cardiol* 1959;**4**:677–85.

6 Fraser RS, Dvorkin J, Rossoll R, Eidem R. Left superior vena cava. A review of associated congenital heart lesions, catheterisation data and roentgenographic findings. *Am J Med* 1961;**31**:711–6.

7 Lenox C, Zuberbuhler JR, Park SC, *et al*. Absent right superior vena cava with persistent left superior vena cava: implications and management. *Am J Cardiol* 1980;**45**:117–22.

8 Pugliese P, Murzi B, Aliboni M, Eufrate S. Absent right superior vena cava and persistent left superior vena cava. Clinical and surgical considerations. *Cardiovasc Surg* 1984;**25**:134–7.

9 Hanlon CR, Barner HB, Willman VL, Mudd JG, Kaiser GC. Atrial septal defect: results of repair in adults. *Arch Surg* 1969;**99**:275–80.

10 Gault JH, Morrow AG, Gay WA Jr, Moss J Jr. Atrial septal defect in patients over the age of forty years. Clinical and haemodynamic studies and the effects of operation. *Circulation* 1968;**37**:261–72.

11 Yalav E, Brown AH, Braimbridge MV. Surgery for atrial septal defect in patients over 60 years of age. Report of surgical correction in 12 patients. *J Thorac Cardiovasc Surg* 1971;**62**:788–92.

Br Heart J 1987;58:678–9

Correspondence

How useful are the cold pressor test and sustained isometric handgrip exercise with radionuclide ventriculography in the evaluation of patients with coronary artery disease?

Sir,
I read with interest the opinions of Northcote and Cooke (1987;57:319–28) on the use of gated blood pool scanning with either isometric handgrip or cold pressor testing for the detection of coronary artery disease.

Giles *et al* used a nuclear probe capable of measuring beat to beat ejection fraction to study these responses and found that troughs in left ventricular ejection fraction occurred at 2·5 min (range 0·5 to 3·0 min) for handgrip and 1·7 min (range 0·5 to 3·0 min) for cold pressor in patients with confirmed coronary disease.[1] Normal controls also had troughs within 3·0 min. There was considerable overlap between patients and controls in terms of both the fall in ejection fraction and the absolute level attained.

Gated blood pool scanning with five minute acquisition seems to be a poor technique for analysing a transient phenomenon with peak effect occurring in less than three minutes. The best that can be measured is an average ejection fraction response. Others have confirmed the time course for cold pressor testing with first pass blood pool scanning[2]; and both isometric handgrip and cold pressor were tested by Jones *et al*,[3] who used a technique similar to that of Giles *et al*.

Use of cold pressor testing or isometric handgrip to detect coronary artery disease is an attractive idea. Unfortunately, with current radionuclide blood pool imaging methods it does not work.

Peter Marx,
1560 East Chevy Chase Drive 355,
Glendale,
CA 91206,
USA.

References

1 Giles G, Marx P, Commerford P, *et al*. Rapid sequential changes in left ventricular function during cold pressor and isometric handgrip: relationship to blood pressure and mechanistic implications [Abstract]. *Am J Cardiol* 1982;49:1002.
2 Dymond DS, Caplin JL, Flatman W, Burnett P, Banim S, Spurrell R. Temporal evolution of changes in left ventricular function induced by cold pressor stimulation. An assessment with radionuclide angiography and gold 195 m. *Br Heart J* 1984;51.557–64.
3 Jones RI, Lahiri A, Cashman PMM, Dore C, Raftery EB. Left ventricular function during isometric hand grip and cold stress in normal subjects. *Br Heart J* 1986;55:246–52.

This letter was shown to Dr Northcote, who replies as follows:

Sir,
Review of our paper evaluating both cold pressor testing and isometric handgrip exercise in conjunction with radionuclide ventriculography shows that we are not at variance with the views of Dr Marx. We clearly conclude from our results that both interventions produce data of poor specificity and sensitivity for the detection of coronary artery disease.

It was not, however, our exclusive remit to examine the usefulness of these tests in the detection of coronary artery disease. We also undertook to establish their viability when used in serial experiments, for example in long term drug studies or in a coronary care setting where repeat scans may be required. Under these circumstances, cold pressor testing and to a lesser extent isometric handgrip did prove to be useful with an acceptable coefficient of variation.

We are of course aware of previous work in this field quoted by Marx and are also aware of the use of the nuclear probe with these interventions, which with its beat to beat variation in ejection fraction has its own intrinsic problems.

It may be a compromise for serial studies to use cold pressor testing or isometric handgrip exercise in conjunction with gamma cameras with a high sensitivity collimator and image for two to three minutes rather than five. Dynamic exercise remains the ideal intervention for this technique, however, when one can be satisfied that movement artefact is not important. Where this is not possible, however, either the cold pressor test or handgrip test may be useful for the serial evaluation of left ventricular performance but not for the detection of coronary artery disease.

Robin J Northcote,
Department of Medical Cardiology,
Victoria Infirmary,
Glasgow.

Br Heart J 1987;58:680

Notices

British Cardiac Society

The Annual General Meeting for 1988 will take place in Belfast on 23 and 24 March 1988, and the closing date for receipt of abstracts will be 4 January 1988.

Asean cardiology

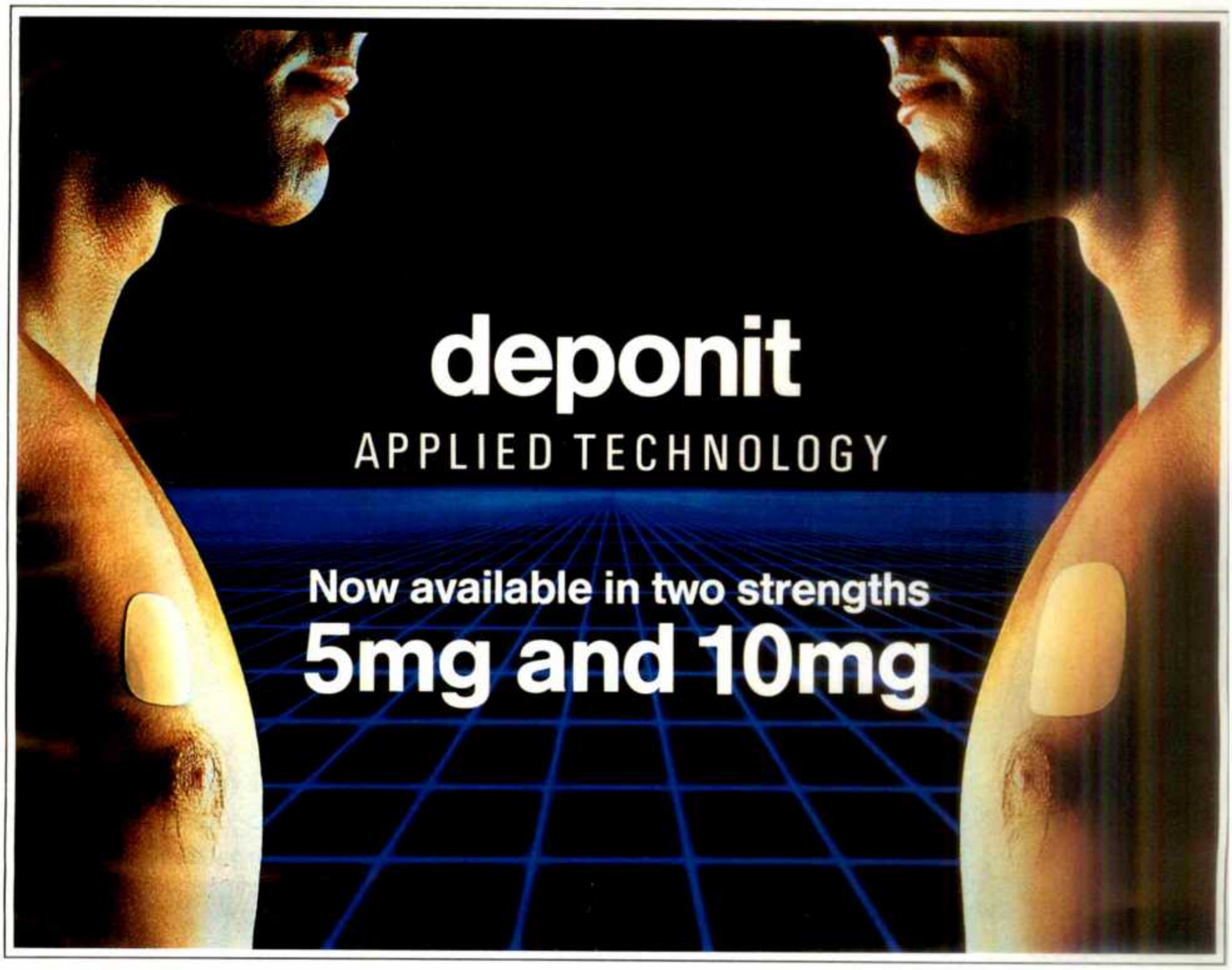
The 7th Asean Congress of Cardiology will be held at the Midtwon Ramada Hotel, Manila, on 24 to 27 February 1988. Inquiries to: Secretariat, The 7th Asean Congress of Cardiology, Philippine Heart Association Inc, c/o Philippine Heart Center, East Avenue, Quezon City, Philippines 1630.

Holter monitoring

The 3rd International Symposium on Holter Monitoring will be held at the Hilton Hotel, Vienna, on 28 to 30 April 1988. Further information from: Dr Heinz Weber, c/o Interconvention, PO Box 80, A-1107 Vienna, Austria.

Cardiology—Moroccan, French, American meeting.

An International Congress of Cardiology, cosponsored by the Council on Clinical Cardiology of the American Heart Association, will be held in Marrakesh on 2 to 5 November 1988. Further information from: Dr M Benomar, Ligue Nationale de Lutte Contre les Maladies Cardiovasculaires, B P 1326, Rabat R P, Marocco; Dr Y Grosgogeat, Groupe Hospitalier Pitié-Salpêtrière, Service de Cardiologie, 47 Boulevard de l'Hôpital, 75013 Paris, France; Dr W C Sheldon, The Cleveland Clinic Foundation, Department of Cardiology, 9500 Euclid Avenue, Cleveland, Ohio 44106, USA.



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Applications for entry must be received by 11 March 1988. Fee £230.

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  septal defect, after myocardial infarction assessment by cross sectional echocardiography with pulsed wave Doppler scanning (MacLeod *et al*). 214
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  stimulation studies in Wolff-Parkinson-White syndrome, uncertainties about interpretation· editorial (Robinson & Krikler). 87
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Wolff-Parkinson-White syndrome
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  uncertainties about interpretation of ventricular stimulation studies; editorial (Robinson & Krikler) 87

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